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STIC Database Tracking Number: 171658

TO: Kevin Weddington Location: 3a65 / 3c70 Tuesday, December 06, 2005 Art Unit: 1614 Phone: 571-272-0587 Serial Number: 10 / 669250	From: Jan Delaval Location: Biotech-Chem Library Remsen 1a51 Phone: 571-272-2504 jan.delaval@uspto.gov

Search Notes

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: K. Weddington Examiner # : 68082 Date: 11-15-05
Art Unit: 1614 Phone Number: 2-0557 Serial Number: 10/669,250
Location (Bldg/Room#): 3A65 (Mailbox #): _____ Results Format Preferred (circle): PAPER DISK
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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: _____

Inventors (please provide full names): Leland Shapiro

_____

Earliest Priority Date: _____

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Inhibiting alpha 1-antitrypsin levels in an animal with ~~a~~ a nitric oxide synthase inhibitor

33. (Original) ~~The method of claim 31~~, in which the nitric oxide synthase inhibitor comprises: N^G-nitro-L-arginine methyl ester, N^G-nitro-L-arginine, N^G-methyl-L-arginine, N,N'-dimethylarginine, N^G-monoethyl-L-arginine acetate, N^G-monomethyl-L-arginine acetate, N^G-monomethyl-D-arginine, N^G-monomethyl-L-homoarginine acetate, N^G-nitro-D-arginine, N^G-nitro-D-arginine methyl ester hydrochloride, ω-nitro-L-arginine, L-N^6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenyleneiodonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N^5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, *p*-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinosydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, S-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or pharmaceutically acceptable free bases thereof, or pharmaceutically acceptable salts thereof.

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Searcher: am
Searcher Phone #: 2254
Searcher Location: _____
Date Searcher Picked Up: 12/6/05
Date Completed: 12/6/05
Searcher Prep & Review Time: 15
Online Time: 5 120

Type of Search
_____ NA Sequence (#)
_____ AA Sequence (#)
✓ Structure (#)
_____ Bibliographic
_____ Litigation
_____ Fulltext
_____ Other

Vendors and cost where applicable
✓ STN _____ Dialog
_____ Questel/Orbit _____ Lexis/Nexis
_____ Westlaw _____ WWW/Internet
____ In-house sequence systems
____ Commercial ____ Oligomer ____ Score/Length
____ Interference ____ SPDI ____ Encode/Transl
_____ Other (specify)

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     (FILE 'HOME' ENTERED AT 08:41:04 ON 06 DEC 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 08:41:17 ON 06 DEC 2005
L1             1 S (US20040220113 OR US20040220239 OR US20040220242)/PN OR (US20
               E SHAPIRO L/AU
L2           281 S E3-E22,E38

     FILE 'REGISTRY' ENTERED AT 08:44:29 ON 06 DEC 2005
L3             1 S 9041-92-3

     FILE 'REGISTRY' ENTERED AT 08:45:08 ON 06 DEC 2005

     FILE 'HCAPLUS' ENTERED AT 08:46:39 ON 06 DEC 2005
L4          5682 S L3
L5           252 S (ALPHA1 OR ALPHA 1)()TRYPSIN(L)INHIBIT?
L6          1636 S (ALPHA1 OR ALPHA 1)()(PROTEASE OR PROTEINASE)(L)INHIBIT?
L7          5862 S (ALPHA1 OR ALPHA 1)()(ANTITRYPSIN OR ANTI TRYPSIN OR ANTIPROT
L8          7762 S L4-L7

     FILE 'REGISTRY' ENTERED AT 08:48:21 ON 06 DEC 2005
               E NITRIC OXIDE/CN
L9             1 S E3
               E NITRIC OXIDE SYNTHASE/CN
L10            1 S E3
L11            3 S E48,E49,E58

     FILE 'HCAPLUS' ENTERED AT 08:49:05 ON 06 DEC 2005
L12        89859 S L9
L13        25812 S L10,L11
L14        30332 S NITRIC OXIDE()(SYNTHASE OR SYNTHETASE)
L15           39 S L8 AND L13,L14
L16           32 S L8 AND L12
L17           72 S L8 AND NITRIC OXIDE
L18           78 S L15-L17
L19            8 S L1,L2 AND L8
L20            4 S L1,L2 AND L12-L14
L21            5 S L1,L2 AND NITRIC OXIDE
L22            9 S L19-L21
               SEL RN L1

     FILE 'REGISTRY' ENTERED AT 08:51:31 ON 06 DEC 2005
L23           83 S E1-E83
L24           80 S L23 NOT L3,L9-L11
L25            1 S L24 AND UNSPECIFIED
L26           79 S L24 NOT L25

     FILE 'HCAPLUS' ENTERED AT 08:56:58 ON 06 DEC 2005
L27            8 S L22 NOT L1
L28            1 S L27 AND CLINICAL CONDITIONS
               SEL RN

     FILE 'REGISTRY' ENTERED AT 09:47:43 ON 06 DEC 2005
L29          117 S E84-E200
L30           19 S 55-63-0 OR 56-06-4 OR 71-44-3 OR 79-17-4 OR 124-20-9 OR 140-6
L31            8 S 53774-63-3 OR 57564-91-7 OR 66036-77-9 OR 74209-34-0 OR 79032
L32           27 S L30,L31
L33            1 S 151-16-6
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L34          40 S 151-16-6/CRN
L35           1 S L34 AND H2O4S
L36           1 S 18144-22-4
L37           1 S L35,L36
L38           1 S 20933-81-7
L39           1 S 36889-13-1
L40           2 S 36889-13-1/CRN
L41           1 S 150403-88-6
L42           1 S 156719-41-4
L43           4 S 156719-41-4/CRN
L44           2 S L43 AND CLH
L45           2 S 2986-19-8 OR 2986-20-1
L46         208 S (2986-19-8 OR 2986-20-1)/CRN
L47           6 S L46 AND H2O4S
                E DIPHENYLENEIODONIUM/CN
L48           1 S E3
L49          44 S 244-54-2/CRN
L50           5 S L49 AND CL/ELS
L51          41 S IC4-C6-C6/ES AND CL/ELS
L52          36 S L51 NOT L50
L53           7 S L52 AND 3/NR AND 1/NC
L54           1 S 75830-53-4
L55          51 S L32,L33,L35,L37-L42,L44,L45,L47,L48,L53,L54
L56          80 S L29 NOT L55
L57          45 S L56 NOT NC4/ES
L58           2 S L57 AND ACETATE
                E NG-MONOETHYL-ARGININE/CN
L59           1 S E6
L60           1 S E2
L61           2 S 20933-81-7/CRN
L62           1 S L61 AND ACETATE
L63           3 S L29 AND CLH
L64           2 S ARGININE/CN
L65           1 S L63 AND NITRO
L66           1 S HOMOARGININE/CN
L67           5 S L29 AND LYSIN?
L68           1 S L67 AND ACETATE
L69           9 S L29 AND NITRO
L70           3 S L69 AND ORNITHINE
L71           1 S L69 AND LYSINE
L72          56 S L55,L58,L60,L62,L65,L68-L70
                E HEMOGLOBIN/CN
L73           1 S E3
                E MYOGLOBIN/CN
                E CYTOCHROME/CN
                E CYTOCHROME 5/CN
                E CYTOCHROME V/CN
L74          57 S L72,L73

     FILE 'HCAPLUS' ENTERED AT 10:15:49 ON 06 DEC 2005
L75       71593 S L74
                SEL DN AN 6
L76         399 S L8 AND L75
L77          11 S L18 AND L76
L78           8 S L77 NOT 3/SC
L79           1 S L1,L2 AND L76
L80           9 S L22,L79
L81           1 S L1,L2 AND L75
L82           9 S L80,L81
L83           7 S L78 NOT L82
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                SEL DN AN 6
L84           1 S L83 AND E1-E3
L85         388 S L76 NOT L77,L82
L86         376 S L85 AND (PY<=2003 OR PRY<=2003 OR AY<=2003)
L87          26 S L74(L)THU/RL AND L86
L88           0 S L87 AND L10,L11
L89           0 S L86 AND L10,L11
L90           0 S L14 AND L86

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FILE LAST UPDATED: 5 Dec 2005  (20051205/ED)

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 This file contains CAS Registry Numbers for easy and accurate
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=> d l84 all hitstr

L84  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:275792  HCAPLUS
DN   131:67664
ED   Entered STN:  05 May 1999
TI   Modulation of peroxynitrite- and hypochlorous acid-induced inactivation of
     .alpha.1-antiproteinase by
     mercaptoethylguanidine
AU   Whiteman, Matthew; Szabo, Csaba; Halliwell, Barry
CS   International Antioxidant Research Centre, Pharmacology Group, Kings
     College, University of London, London, SW3 6LX, UK
SO   British Journal of Pharmacology (1999), 126(7), 1646-1652
     CODEN: BJPCBM; ISSN: 0007-1188
PB   Stockton Press
DT   Journal
LA   English
CC   1-4 (Pharmacology)
AB   Peroxynitrite is a cytotoxic species that can be formed, among other
     mechanisms, by the rapid reaction of superoxide with nitric
     oxide. Peroxynitrite formation has been implicated in a wide
     range of neurodegenerative and chronic inflammatory diseases, as has the
     formation of hypochlorous acid by myeloperoxidase. There is considerable
     interest in the development of peroxynitrite scavengers as therapeutic
     agents. The thiol compound mercaptoethylguanidine has been suggested to
     fulfil this role since it has recently been shown to be not only a potent
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inhibitor of inducible **nitric oxide synthase** but also a scavenger of peroxynitrite. Indeed, it has been shown to be protective in some exptl. models of circulatory shock and inflammation at plasma levels in the approx. range 100-300 μM. One protein inactivated by peroxynitrite is the major inhibitor of serine proteinases in human body fluids, **.alpha.1-antiproteinase**. At high (250-1000 μM) concns., mercaptoethylguanidine was found to be effective in preventing peroxynitrite-mediated tyrosine nitration and α1-AP inactivation. By contrast, lower concns. of mercaptoethylguanidine (1-60 μM) enhanced the inactivation of . **alpha.1-antiproteinase** by peroxynitrite. At all concns. tested (1 - 1000 μM), mercaptoethylguanidine decreased the inactivation of **.alpha.1-antiproteinase** by hypochlorous acid. We suggest that products of reaction of mercaptoethylguanidine with peroxynitrite or peroxynitrite-derived products could cause damage to **.alpha.1-antiproteinase**, and possibly other proteins in vivo, whereas scavenging of hypochlorous acid by mercaptoethylguanidine could contribute to its anti-inflammatory action in vivo.

ST mercaptoethylguanidine peroxynitrite hypochlorous acid interaction antiproteinase; **nitric oxide** iNOS peroxynitrite scavenger mercaptoethylguanidine; alfa1 antiproteinase mercaptoethylguanidine peroxynitrite antiinflammatory hypochlorate

IT Anti-inflammatory agents
Drug interactions
Scavengers
(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of α **1-antiproteinase** by mercaptoethylguanidine)

IT **1190-74-5**, Mercaptoethylguanidine 7790-92-3, Hypochlorous acid 19059-14-4, Peroxynitrite
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of α **1-antiproteinase** by mercaptoethylguanidine)

IT **9041-92-3**, α **1-Antiproteinase**
10102-43-9, **Nitric oxide**, biological studies
125978-95-2, **Nitric oxide synthase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of α **1-antiproteinase** by mercaptoethylguanidine)

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD

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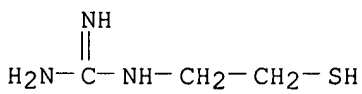
IT **1190-74-5**, Mercaptoethylguanidine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of α **1-antiproteinase** by mercaptoethylguanidine)

RN 1190-74-5 HCAPLUS
CN Guanidine, (2-mercaptoethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



IT **9041-92-3**, α **1-Antiproteinase**
10102-43-9, **Nitric oxide**, biological studies
125978-95-2, **Nitric oxide synthase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of peroxynitrite- and hypochlorous acid-induced inactivation of α **1-antiproteinase** by mercaptoethylguanidine)

RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N═O

RN 125978-95-2 HCAPLUS
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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L82 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:968910 HCAPLUS
DN 143:222096
TI **.alpha.1-Antitrypsin** monotherapy prolongs islet allograft survival in mice
AU Lewis, Eli C.; **Shapiro, Leland**; Bowers, Owen J.; Dinarello, Charles A.
CS Department of Medicine, University of Colorado at Denver and Health Sciences Center, Denver, CO, 80262, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2005), 102(34), 12153-12158
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Islet transplantation for type 1 diabetic patients shows promising results with the use of nondiabetogenic immunosuppressive therapy. However, in addition to compromising the immune system of transplant recipients, long-term studies demonstrate that islet viability is impaired. Here, we demonstrate that, in the absence of immunosuppressive agents, monotherapy with clin.-grade human **.alpha.1-antitrypsin** (hAAT), the major serum serine-protease inhibitor, prolongs islet graft survival and normoglycemia in transplanted allogeneic diabetic mice, lasting until the development of anti-hAAT antibodies. Compared to untreated or albumin-control-treated graft recipients, which rejected islets at day 10, AAT-treated mice displayed diminished cellular infiltrates and intact intragraft insulin production throughout treatment. Using peritoneal infiltration models, we demonstrate that AAT decreases allogeneic fibroblast-elicited natural-killer-cell influx by 89%, CD3-pos. cell influx by 44%, and thioglycolate-elicited neutrophil emigration by 66%. ATT also extended islet viability in mice after streptozotocin-induced beta cell toxicity. In vitro, several islet responses to IL-1β/IFNγ stimulation were examined In the presence of AAT, islets displayed enhanced viability and inducible insulin secretion. Islets also released 36% less **nitric oxide** and 82% less macrophage inflammatory protein 1 α and expressed 63% fewer surface MHC class II mols. TNFα release from IL-1β/IFN-γ-stimulated islet cells was reduced by 99%, accompanied by an 8-fold increase in the accumulation of membrane TNFα on CD45-pos. islet cells. In light of the established safety record and the nondiabetogenic potential of AAT, these data suggest that AAT may be beneficial as adjunctive therapy in patients undergoing islet transplantation.
IT **9041-92-3, α 1-Antitrypsin**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α **1-antitrypsin** monotherapy
prolongs islet allograft survival in mice)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
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L82 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2005:182815 HCAPLUS
DN 142:273969
TI Inhibitors of serine protease activity and their use in methods and compositions for treatment of bacterial infections
IN **Shapiro, Leland**
PA The Regents of the University of Colorado, USA
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005019434	A2	20050303	WO 2004-US27711	20040826
	WO 2005019434	A3	20051006		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005106151	A1	20050519	US 2004-926051	20040826
PRAI	US 2003-497703P	P	20030826		

AB A method for treating and preventing bacterial diseases is provided. In particular, the invention provides compns. and methods for inhibition of Gram neg., Gram pos. and acid fast bacilli in general and tuberculosis (TB), mycobacterium avium complex (MAC), and anthrax in particular. The invention relates to modulation of cellular activities, including macrophage activity, and the like. More particularly, the invention relates to the inhibitory compds. comprising naturally occurring and man-made inhibitors of serine protease. Inhibitors of the invention include **.alpha.1-antitrypsin.**

IT **10102-43-9, Nitric oxide**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serine protease inhibitors for treatment of bacterial infections)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N═O

IT **9041-92-3, α 1-Antitrypsin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of bacterial infections)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L82 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:934333 HCAPLUS
DN 141:388760
TI Inhibitors of serine protease activity, methods and compositions for

treatment of **nitric oxide** induced clinical conditions
IN **Shapiro, Leland**
PA USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004220242	A1	20041104	US 2003-427929	20030502 <--
	US 2004220113	A1	20041104	US 2003-669250	20030925 <--
	US 2004220239	A1	20041104	US 2003-669251	20030925 <--
PRAI	US 2003-427929	A3	20030502 <--		

AB A novel method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases associated with aberrant levels of **nitric oxide** and facilitated by a serine proteolytic (SP) activity are disclosed, which consist of administering to a subject a therapeutically effective amount of a compound having a serine protease inhibitory activity. Among effective compds. are **.alpha .1-antitrypsin** and synthetic drugs mimicking some or all of the actions of **.alpha.1-antitrypsin**.
IT **10102-43-9, Nitric oxide**, biological studies
501433-35-8, Inducible **nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of serine protease activity, methods and compns. for treatment of **nitric oxide** induced pathol. conditions)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N═O

RN 501433-35-8 HCAPLUS
CN Synthase, nitric oxide, 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9041-92-3, α 1-Antitrypsin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of serine protease activity, methods and compns. for treatment of **nitric oxide** induced pathol. conditions)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L82 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:120425 HCAPLUS
DN 134:305011
TI **Alpha-1-antitrypsin** inhibits human immunodeficiency virus type 1
AU **Shapiro, Leland**; Pott, Gregory B.; Ralston, Annemarie H.
CS Department of Medicine, Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SO FASEB Journal (2001), 15(1), 115-122

CODEN: FAJOEC; ISSN: 0892-6638
PB Federation of American Societies for Experimental Biology
DT Journal
LA English
AB Several observations suggest the existence of potent endogenous suppressors of human immunodeficiency virus type 1 (HIV-1) production, and inhibitors of serine proteases may participate in this effect. **Alpha-1-antitrypsin** (AAT) is the most abundant circulating serine protease inhibitor. Physiol. AAT concns. inhibited HIV-1 production in chronically infected U1 monocytic cells, reduced virus replication in freshly infected peripheral blood mononuclear cells, and blocked infection of permissive HeLa cells. In U1 cells, AAT suppressed activation of the HIV-1-inducing transcription factor NF-κB. Similar results were obtained using CE-2072, a synthetic inhibitor of host serine proteases. HIV-1 did not replicate in blood obtained from healthy volunteers, but marked replication was observed in blood from individuals with hereditary AAT deficiency. These results identify AAT as a candidate circulating HIV-1 inhibitor in vivo. Two different mechanisms of AAT-induced HIV-1 inhibition were identified, including reduced HIV-1 infectivity and blockade of HIV-1 production A novel host-pathogen interaction is suggested, and an alternative strategy to treat HIV-1-related disease may be possible.
IT **9041-92-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**alpha-1-antitrypsin** inhibits HIV-1)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Avril, L	1993	317	167	FEBS Lett	HCAPLUS
Avril, L	1994	345	81	FEBS Lett	HCAPLUS
Bayliss, G	1990	31	161	J Med Virol	MEDLINE
Blank, C	1994	72	105	Ann Allergy	HCAPLUS
Bristow, C	1995	7	239	Int Immunol	HCAPLUS
Bush, C	1996	13	23	J AIDS	MEDLINE
Carpenter, C	2000	283	381	J Am Med Assoc	MEDLINE
Carrell, R	1986	78	1427	J Clin Invest	HCAPLUS
Coan, M	1985	48	333	Vox Sang	HCAPLUS
Coeshott, C	1999	96	6261	Proc Natl Acad Sci	HCAPLUS
Crystal, R	1990	85	1343	J Clin Invest	HCAPLUS
Dimitrov, D	1990	28	734	J Clin Microbiol	MEDLINE
Donovan, R	1996	174	401	J Infect Dis	MEDLINE
Duh, E	1989	86	5974	Proc Natl Acad Sci	HCAPLUS
Embretson, J	1993	362	359	Nature	MEDLINE
Fiore, J	1990	13	311	Microbiologica	MEDLINE
Folks, T	1987	238	800	Science	HCAPLUS
Fox, P	1988	116	635	J Am Dental Assoc	MEDLINE
Gass, R	1998	3	97	Antiviral Ther	HCAPLUS
Gu, Y	1997	275	206	Science	HCAPLUS
Hattori, T	1989	248	48	FEBS Lett	HCAPLUS
Henderson, D	1990	113	740	Ann Int Med	MEDLINE
Japour, A	1994	32	2291	J Clin Microbiol	MEDLINE
Jeppsson, J	1976	65	195	FEBS Lett	HCAPLUS
Keet, I	1991	6	223	AIDS	

Kido, H	1991	286	233	FEBS Lett	HCAPLUS
Kido, H	1990	265	21979	J Biol Chem	HCAPLUS
Kimpton, J	1992	66	2232	J Virol	HCAPLUS
Kingsley, L	1987	1	345	Lancet	MEDLINE
Larder, B	1989	243	1731	Science	HCAPLUS
Lenardo, M	1989	58	227	Cell	HCAPLUS
Lyman, D	1986	255	1703	J Am Med Assoc	MEDLINE
Massi, G	1994	393	1	Acta Paediatr	
Mayer, K	1987	107	428	Ann Int Med	
McNeely, T	1997	90	1141	Blood	HCAPLUS
McNeely, T	1995	96	456	J Clin Invest	HCAPLUS
Narayanam, V	1991	266	9540	J Biol Chem	
Osborn, L	1989	86	2336	Proc Natl Acad Sci	HCAPLUS
Pantaleo, G	1993	362	355	Nature	MEDLINE
Poli, G	1990	172	151	J Exp Med	HCAPLUS
Shapiro, L	1995	92	12230	Proc Natl Acad Sci	HCAPLUS
Shapiro, L	1998	95	12550	Proc Natl Acad Sci	HCAPLUS
Shapiro, L	1998	95	7422	Proc Natl Acad Sci	HCAPLUS
Stoller, R	1997	111	123S	Chest	
Tiffany, T	1987		74	Fundamentals of Clin	
Tokars, J	1993	118	913	Ann Int Med	MEDLINE
Werner, B	1982	97	367	Ann Int Med	MEDLINE
Wewers, M	1987	316	1055	N Engl J Med	MEDLINE
Winkelstein, W	1987	257	321	J Am Med Assoc	

L82 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:628160 HCAPLUS
DN 133:232870
TI Inhibitors of serine protease activity, and methods and compositions for treatment of viral infections and other conditions
IN **Shapiro, Leland**
PA The Trustees of University Technology Corp., USA
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000052034	A2	20000908	WO 2000-US5558	20000303
	WO 2000052034	A3	20010111		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000037191	A5	20000921	AU 2000-37191	20000303
	US 6849605	B1	20050201	US 2000-518098	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-137795P	P	19990603		
	WO 2000-US5558	W	20000303		

OS MARPAT 133:232870
AB A method of treating and preventing viral infection is provided. In particular, a method of blocking viral infection facilitated by a serine proteolytic activity is disclosed, which consists of administering to a subject suffering or about to suffer from viral infection a

therapeutically effective amount of a compound having a serine protease inhibitory or serpin activity. Among compds. are α **1-antitrypsin** (AAT), peptide derivs. from the carboxyterminal end of AAT, and man-made, synthetic compds. mimicking the action of such compds. The preferred viral infections include retroviral infection such as human immunodeficiency virus (HIV) infection. A method for treating other pathol. conditions mediated my a serine protease is also disclosed.

IT **9041-92-3, α 1-Antitrypsin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(serine protease inhibitors for treatment of viral infections and other conditions, and use with other agents)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L82 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:628010 HCAPLUS
DN 133:217681
TI Inhibitors of serine protease activity, and methods and compositions for treatment of herpes virus infections
IN **Shapiro, Leland**
PA The Trustees of University Technology Corporation, USA
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051625	A1	20000908	WO 2000-US5557	20000303
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000038640	A5	20000921	AU 2000-38640	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-153942P	P	19990915		
	WO 2000-US5557	W	20000303		

OS MARPAT 133:217681
AB Compns. and methods of treating and preventing a viral infection are provided. A method of blocking a viral infection facilitated by a serine proteolytic (SP) activity is disclosed, which involves administering to a subject suffering or about to suffer from a viral infection a therapeutically effective amount of a substance having serine protease inhibitory activity or serpin activity. Among the substances found to be useful are **.alpha.1-antitrypsin** (AAT), peptide derivs. from the carboxy terminal end of AAT and synthetic drugs mimicking the action of such substances. The invention is particularly well suited for checking a viral infection mediated by members of herpesviridae family.
IT **9041-92-3, α 1 Antitrypsin**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Cortech	1998			WO 9824806 A	HCAPLUS
Emory University	1998			WO 9846597 A	HCAPLUS
Lezdey, J	1994			WO 9407525 A	HCAPLUS

L82 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:628009 HCAPLUS
DN 133:217725
TI Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof
IN **Shapiro, Leland**
PA The Trustees of University Technology Corporation, USA
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051624	A2	20000908	WO 2000-US6069	20000303
	WO 2000051624	A3	20001228		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000037314	A5	20000921	AU 2000-37314	20000303
PRAI	US 1999-123167P	P	19990305		
	WO 2000-US6069	W	20000303		

AB A method is provided for treating an animal suffering a disease characterized by excessive apoptosis by administering a therapeutically effective amount of at least one serine protease inhibitor and thereafter monitoring a decrease in apoptosis. The inhibitor of the invention includes .**alpha.1-antitrypsin** or an . **alpha.1-antitrypsin**-like agent, including but not limited to oxidation-resistant variants of .**alpha.1-antitrypsin**, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, autoimmune disease, sepsis neurodegenerative disease, myocardial infarction, stroke, ischemia-reperfusion injury, toxin induced liver injury and AIDS. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by excessive apoptosis.
IT **9041-92-3, α 1 Antitrypsin**
9041-92-3D, α 1 Antitrypsin,

variants
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for inhibiting apoptosis, and therapeutic use)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

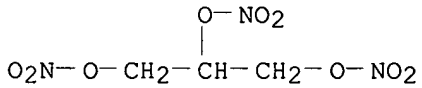
L82 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:628008 HCAPLUS
DN 133:217724
TI Inhibitors of serine protease activity, and methods and compositions for treatment of **nitric oxide**-induced clinical conditions
IN **Shapiro, Leland**
PA The Trustees of University Technology Corp., USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051623	A2	20000908	WO 2000-US5556	20000303
	WO 2000051623	A3	20001214		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000035115	A5	20000921	AU 2000-35115	20000303
	US 6489308	B1	20021203	US 2000-518097	20000303
PRAI	US 1999-123167P	P	19990305		
	US 1999-156523P	P	19990929		
	WO 2000-US5556	W	20000303		

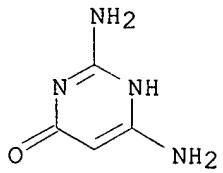
AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases associated with aberrant levels of **nitric oxide** and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amount of a compound having a serine protease inhibitory activity. Among effective compds. are α **1-antitrypsin** and synthetic drugs mimicking some or all of the actions of **.alpha.1-antitrypsin.**
IT **125978-95-2, Nitric oxide synthase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)
RN 125978-95-2 HCAPLUS
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9001-92-7**, Protease
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitory; serine protease inhibitors for treatment of NO-induced diseases)
RN 9001-92-7 HCAPLUS
CN Proteinase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **55-63-0**, Nitroglycerine **56-06-4**, 2,4-Diamino-6-hydroxypyrimidine **71-44-3**, Spermine **79-17-4**, Aminoguanidine **124-20-9**, Spermidine **140-64-7**, Pentamidine isethionate **151-16-6 298-83-9**, p-Nitroblue tetrazolium chloride **867-44-7 1071-37-0**, 2-Ethyl-2-thiopseudourea hydrobromide **1190-74-5**, Mercaptoethylguanidine **2149-70-4 2751-09-9**, Troleandomycin **2942-42-9**, 7-Nitroindazole **2986-19-8**, S-Methylisothiourea **2986-20-1**, S-Ethylisothiourea **9041-92-3**, α **1-Antitrypsin** **13395-35-2**, 2-Iminobiotin **17035-90-4 18144-22-4** **20933-81-7 21835-19-8 22722-03-8**, S-Ethylisothiourea sulfate **25769-03-3**, 1-Pyrrolidinecarbodithioic acid **30344-00-4 33876-97-0** **36889-13-1 50912-92-0 53774-63-3** **57564-91-7**, S-Nitroso-glutathione **66036-77-9**, NG-Nitro-D-arginine **74209-34-0**, 3-Bromo-7-nitroindazole **75830-53-4 79032-48-7**, S-Nitroso-N-acetylpenicillamine **133587-00-5**, NG-Monomethyl-L-arginine acetate **137694-74-7** **150403-88-6 156719-37-8**, L-Thiocitrulline **156719-41-4**, S-Methyl-L-thiocitrulline **209248-80-6** **209248-86-2 209589-59-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)
RN 55-63-0 HCAPLUS
CN 1,2,3-Propanetriol, trinitrate (9CI) (CA INDEX NAME)



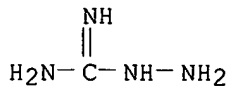
RN 56-06-4 HCAPLUS
CN 4(1H)-Pyrimidinone, 2,6-diamino- (8CI, 9CI) (CA INDEX NAME)



RN 71-44-3 HCAPLUS
CN 1,4-Butanediamine, N,N'-bis(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)

$H_2N-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$

RN 79-17-4 HCAPLUS
CN Hydrazinecarboximidamide (9CI) (CA INDEX NAME)



RN 124-20-9 HCAPLUS
CN 1,4-Butanediamine, N-(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)

$H_2N-(CH_2)_4-NH-(CH_2)_3-NH_2$

RN 140-64-7 HCAPLUS
CN Ethanesulfonic acid, 2-hydroxy-, compd. with 4,4'-[1,5-pentanediylbis(oxy)]bis[benzenecarboximidamide] (2:1) (9CI) (CA INDEX NAME)

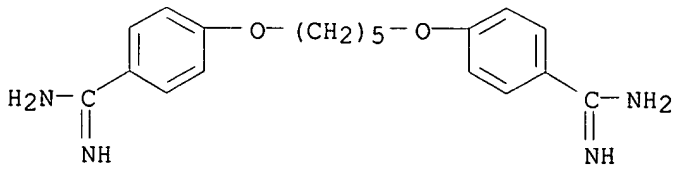
CM 1

CRN 107-36-8
CMF C2 H6 O4 S

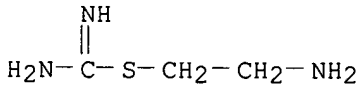
$HO-CH_2-CH_2-SO_3H$

CM 2

CRN 100-33-4
CMF C19 H24 N4 O2

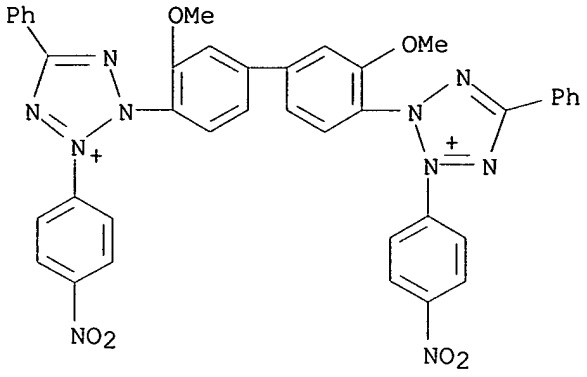


RN 151-16-6 HCAPLUS
CN Carbamimidothioic acid, 2-aminoethyl ester (9CI) (CA INDEX NAME)



RN 298-83-9 HCAPLUS

CN 2H-Tetrazolium, 2,2'-(3,3'-dimethoxy[1,1'-biphenyl]-4,4'-diyl)bis[3-(4-nitrophenyl)-5-phenyl-, dichloride (9CI) (CA INDEX NAME)

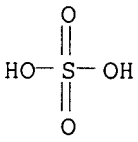


●2 Cl^-

RN 867-44-7 HCAPLUS
CN Carbamimidothioic acid, methyl ester, sulfate (2:1) (9CI) (CA INDEX NAME)

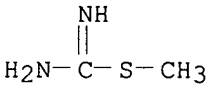
CM 1

CRN 7664-93-9
CMF H2 O4 S

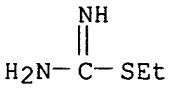


CM 2

CRN 2986-19-8
CMF C2 H6 N2 S

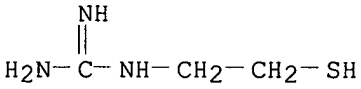


RN 1071-37-0 HCAPLUS
CN Carbamimidothioic acid, ethyl ester, monohydrobromide (9CI) (CA INDEX NAME)



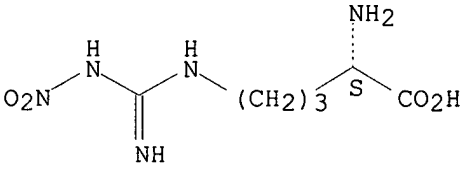
● HBr

RN 1190-74-5 HCAPLUS
CN Guanidine, (2-mercaptoethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



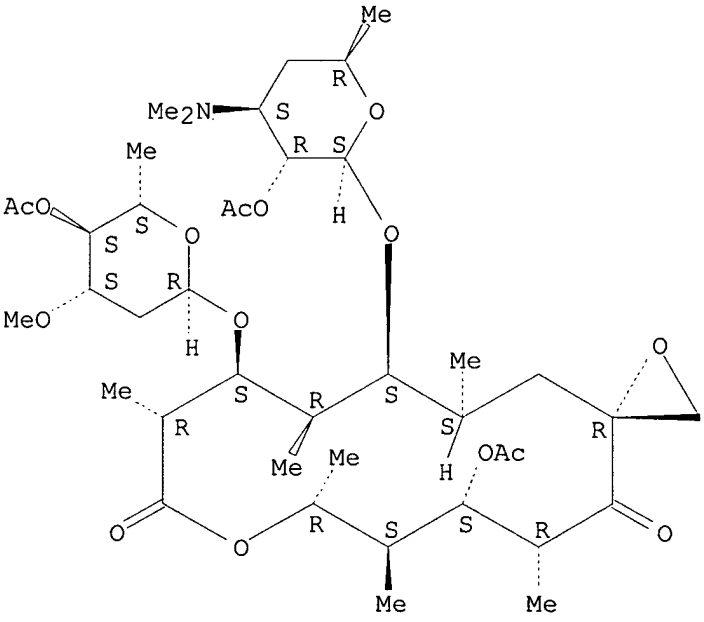
RN 2149-70-4 HCAPLUS
CN L-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

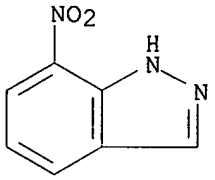


RN 2751-09-9 HCAPLUS
CN Oleandomycin, triacetate (ester) (8CI, 9CI) (CA INDEX NAME)

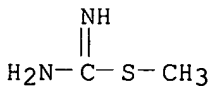
Absolute stereochemistry.



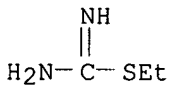
RN 2942-42-9 HCAPLUS
CN 1H-Indazole, 7-nitro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 2986-19-8 HCAPLUS
CN Carbamimidothioic acid, methyl ester (9CI) (CA INDEX NAME)



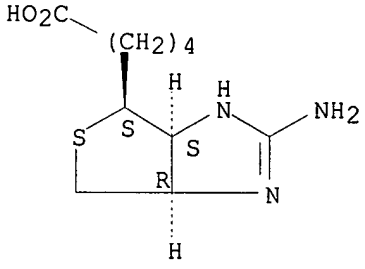
RN 2986-20-1 HCAPLUS
CN Carbamimidothioic acid, ethyl ester (9CI) (CA INDEX NAME)



RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

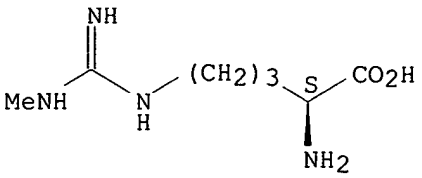
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 13395-35-2 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, 2-amino-3a,4,6,6a-tetrahydro-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 17035-90-4 HCAPLUS
CN L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

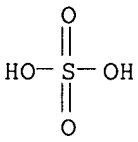
Absolute stereochemistry.



RN 18144-22-4 HCAPLUS
CN Carbamimidothioic acid, 2-aminoethyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

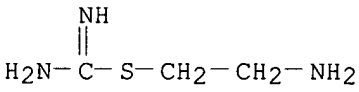
CM 1

CRN 7664-93-9
CMF H2 O4 S



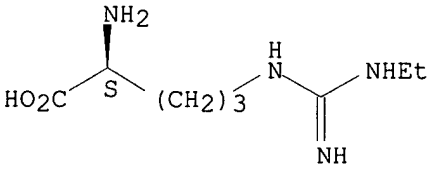
CM 2

CRN 151-16-6
CMF C3 H9 N3 S



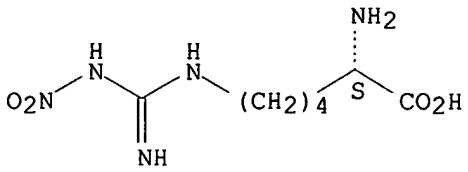
RN 20933-81-7 HCAPLUS
CN L-Ornithine, N5-[(ethylamino)iminomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 21835-19-8 HCAPLUS
CN L-Lysine, N6-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

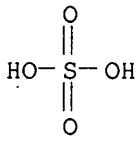
Absolute stereochemistry.



RN 22722-03-8 HCAPLUS
CN Carbamimidothioic acid, ethyl ester, sulfate (1:1) (9CI) (CA INDEX NAME)

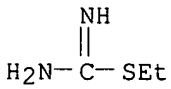
CM 1

CRN 7664-93-9
CMF H2 O4 S

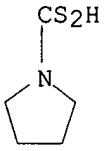


CM 2

CRN 2986-20-1
CMF C3 H8 N2 S

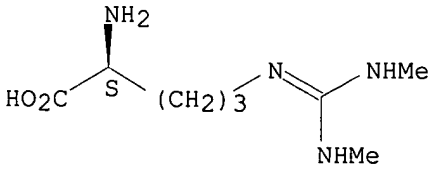


RN 25769-03-3 HCAPLUS
CN 1-Pyrrolidinecarbodithioic acid (7CI, 8CI, 9CI) (CA INDEX NAME)

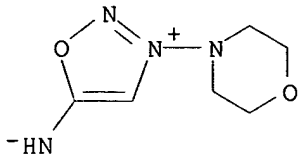


RN 30344-00-4 HCAPLUS
CN L-Ornithine, N5-[bis(methylamino)methylene]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

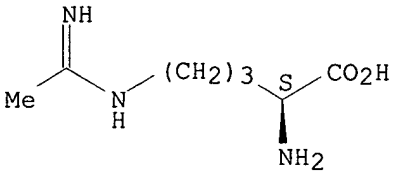


RN 33876-97-0 HCAPLUS
CN 1,2,3-Oxadiazolium, 5-amino-3-(4-morpholinyl)-, inner salt (9CI) (CA INDEX NAME)



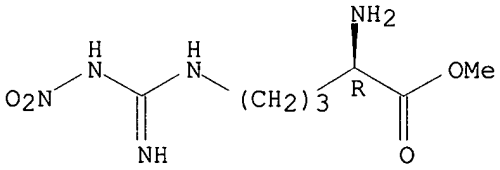
RN 36889-13-1 HCAPLUS
CN L-Ornithine, N5-(1-iminoethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 50912-92-0 HCAPLUS
CN D-Ornithine, N5-[imino(nitroamino)methyl]-, methyl ester, monohydrochloride (9CI) (CA INDEX NAME)

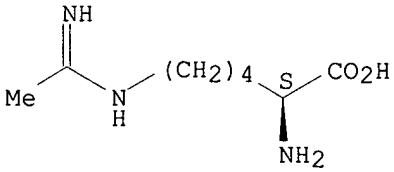
Absolute stereochemistry.



● HCl

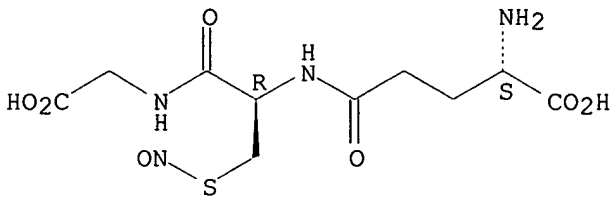
RN 53774-63-3 HCAPLUS
CN L-Lysine, N6-(1-iminoethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



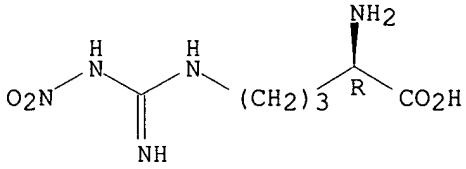
RN 57564-91-7 HCAPLUS
CN Glycine, L-γ-glutamyl-S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

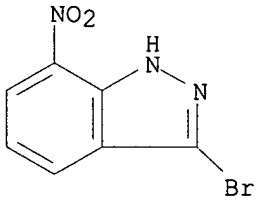


RN 66036-77-9 HCAPLUS
CN D-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

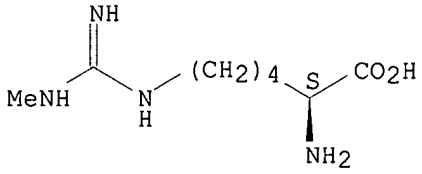


RN 74209-34-0 HCAPLUS
CN 1H-Indazole, 3-bromo-7-nitro- (9CI) (CA INDEX NAME)



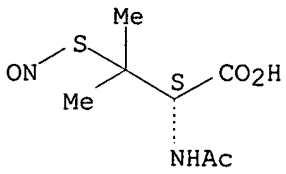
RN 75830-53-4 HCAPLUS
CN L-Lysine, N6-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79032-48-7 HCAPLUS
CN D-Valine, N-acetyl-3-(nitrosothio)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

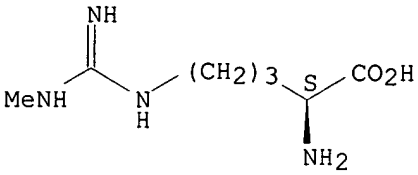


RN 133587-00-5 HCAPLUS
CN L-Ornithine, N5-[imino(methylamino)methyl]-, acetate (9CI) (CA INDEX NAME)

CM 1

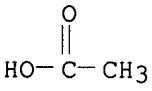
CRN 17035-90-4
CMF C7 H16 N4 O2

Absolute stereochemistry.



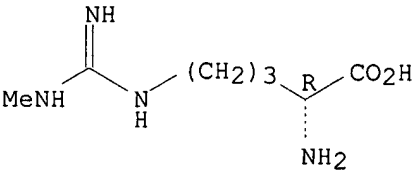
CM 2

CRN 64-19-7
CMF C2 H4 O2



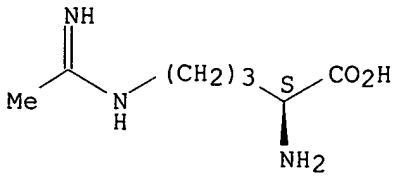
RN 137694-74-7 HCAPLUS
CN D-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 150403-88-6 HCAPLUS
CN L-Ornithine, N5-(1-iminoethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

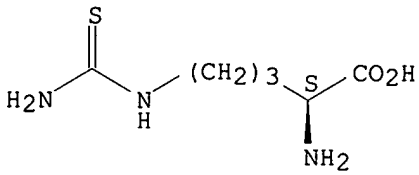
Absolute stereochemistry.



● HCl

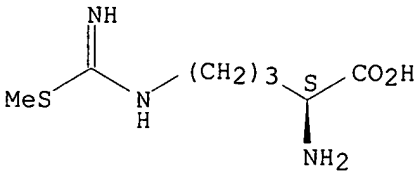
RN 156719-37-8 HCAPLUS
CN L-Ornithine, N5-(aminothioxomethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156719-41-4 HCAPLUS
CN L-Ornithine, N5-[imino(methylthio)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

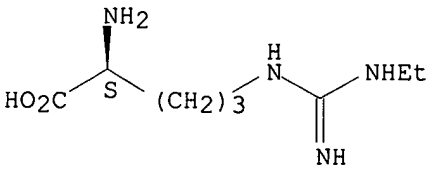


RN 209248-80-6 HCAPLUS
CN L-Ornithine, N5-[(ethylamino)iminomethyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

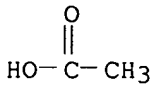
CRN 20933-81-7
CMF C8 H18 N4 O2

Absolute stereochemistry.



CM 2

CRN 64-19-7
CMF C2 H4 O2

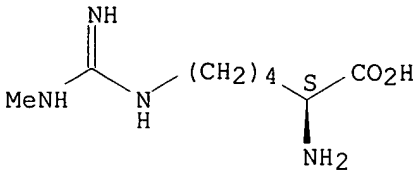


RN 209248-86-2 HCAPLUS
CN L-Lysine, N6-[imino(methylamino)methyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

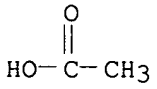
CRN 75830-53-4
CMF C8 H18 N4 O2

Absolute stereochemistry.



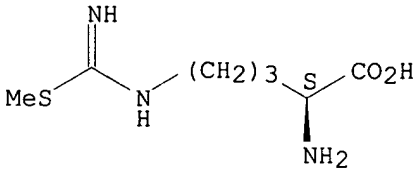
CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 209589-59-3 HCAPLUS
CN L-Ornithine, N5-[imino(methylthio)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



●2 HCl

IT **10102-43-9, Nitric oxide**, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors for treatment of NO-induced diseases)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

L82 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:403996 HCAPLUS
DN 129:135005
TI Interleukin-1β-induced rat pancreatic islet **nitric oxide** synthesis requires both the p38 and extracellular signal-regulated kinase 1/2 mitogen-activated protein kinases
AU Larsen, Claus M.; Wadt, Karin A. W.; Juhl, Lone F.; Andersen, Henrik U.; Karlsen, Allan E.; Su, Michael S.-S.; Seedorf, Klaus; **Shapiro, Leland**; Dinarello, Charles A.; Mandrup-Poulsen, Thomas
CS Univ. Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Journal of Biological Chemistry (1998), 273(24), 15294-15300
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Interleukin-1β (IL-1β) is cytotoxic to rat pancreatic β-cells by inhibiting glucose oxidation, causing DNA damage, and inducing apoptosis. **Nitric oxide** (NO) is a necessary but not sufficient mediator of these effects. IL-1β induced kinase activity toward Elk-1, activation transcription factor 2, c-Jun, and heat shock protein 25 in rat islets. By Western blotting with phosphospecific antibodies and by immunocomplex kinase assay, IL-1β was shown to activate extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (p38) in islets and rat insulinoma cells. Specific ERK1/2 and p38 inhibitors individually reduced but in combination blocked IL-1β-mediated islet NO synthesis, and reverse transcription-polymerase chain reaction of inducible NO synthase mRNA showed that ERK1/2 and p38 controlled IL-1β-induced islet inducible NO synthase expression at the transcriptional level. Hyperosmolarity caused phosphorylation of Elk-1, activation of transcription factor 2, and heat shock protein 25, and activation of ERK1/2 and p38 in islets comparable to that induced by IL-1β but did not lead to NO synthesis. Inhibition of p38 but not of ERK1/2 attenuated IL-1β-mediated inhibition of glucose-stimulated insulin release. Thus, ERK1/2 and p38 activation is necessary but not sufficient for IL-1β-mediated β-cell NO synthesis and p38 is involved in signaling of NO-independent effects of IL-1β in β-cells.
IT **10102-43-9, Nitric oxide**, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(ERK1/2 and p38 kinases activation is necessary but not sufficient for interleukin-1β-mediated β-cell **nitric oxide** formation and p38 is involved in signaling of NO-independent effects of IL-1β in pancreatic β-cells)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Akabane, A	1995	215	524	Biochem Biophys Res	HCAPLUS
Alessi, D	1995	270	27489	J Biol Chem	HCAPLUS
Andersen, H	1994	43	770	Diabetes	HCAPLUS
Angel, P	1991	1072	129	Biochim Biophys Acta	HCAPLUS
Ankarcrona, M	1994	213	172	Exp Cell Res	HCAPLUS
Beyaert, R	1996	15	1914	EMBO J	MEDLINE
Brunstedt, J	1984		254	Methods in Diabetes	
Cano, E	1995	20	117	TIBS	HCAPLUS
Cao, Z	1996	271	1128	Science	HCAPLUS
Corbett, J	1992	41	897	Diabetes	HCAPLUS
Corbett, J	1993	7	369	FASEB J	HCAPLUS
Corbett, J	1995	181	559	J Exp Med	HCAPLUS
Corbett, J	1993	90	1731	Proc Natl Acad Sci U	HCAPLUS
Cuenda, A	1995	364	229	FEBS Lett	HCAPLUS
Da Silva, J	1997	272	28373	J Biol Chem	HCAPLUS
Dudley, D	1995	92	7686	Proc Natl Acad Sci U	HCAPLUS
Eizirik, D	1992	308	249	FEBS Lett	HCAPLUS
Graves, J	1996	93	13814	Proc Natl Acad Sci U	HCAPLUS
Green, L	1982	126	131	Anal Biochem	HCAPLUS
Guan, Z	1997	272	8083	J Biol Chem	HCAPLUS
Gupta, S	1995	267	389	Science	HCAPLUS
Hazzalin, C	1997	15	2321	Oncogene	HCAPLUS
Heding, L	1972	8	260	Diabetologia	HCAPLUS
Hill, C	1995	80	199	Cell	HCAPLUS
Ichijo, H	1997	275	90	Science	HCAPLUS
Jensen, J	1996	271	18749	J Biol Chem	HCAPLUS
Jiang, Y	1996	271	17920	J Biol Chem	HCAPLUS
Kaneto, H	1995	44	733	Diabetes	HCAPLUS
Khoo, S	1997	94	5599	Proc Natl Acad Sci U	HCAPLUS
Kinugawa, K	1997	81	911	Circ Res	HCAPLUS
Kwon, G	1995	136	4790	Endocrinology	HCAPLUS
Laemmli, U	1970	227	680	Nature	HCAPLUS
Lee, J	1994	372	739	Nature	HCAPLUS
Mandrup-Poulsen, T	1987	95	55	APMIS	MEDLINE
Mandrup-Poulsen, T	1996	39	1005	Diabetologia	HCAPLUS
Mendelson, K	1996	23	12908	Proc Natl Acad Sci U	
Muller, J	1997	272	23435	J Biol Chem	HCAPLUS
Pandey, P	1996	271	23775	J Biol Chem	HCAPLUS
Rabinovitch, A	1990	71	152	J Clin Endocrinol Me	HCAPLUS
Raingeaud, J	1995	270	7420	J Biol Chem	HCAPLUS
Reimers, J	1996	45	771	Diabetes	HCAPLUS
Saklatvala, J	1996	271	6586	J Biol Chem	HCAPLUS
Saldeen, J	1994	203	149	Biochem Biophys Res	HCAPLUS
Sandler, S	1989	124	1492	Endocrinology	HCAPLUS
Seedorf, K	1994	269	16009	J Biol Chem	HCAPLUS
Shapiro, L	1995	92	12230	Proc Natl Acad Sci U	HCAPLUS
Singh, K	1996	271	1111	J Biol Chem	HCAPLUS
Tan, Y	1996	15	4629	EMBO J	HCAPLUS
Uciechowski, P	1996	394	273	FEBS Lett	HCAPLUS
Verheij, M	1996	380	75	Nature	HCAPLUS
Waskiewicz, A	1995	7	798	Curr Opin Cell Biol	HCAPLUS
Welsh, N	1994	14	43	Biosci Rep	HCAPLUS

Welsh, N	1996	271	8307	J Biol Chem	HCAPLUS
Wesselborg, S	1997	272	12422	J Biol Chem	HCAPLUS
Whitmarsh, A	1995	269	403	Science	HCAPLUS
Xia, Z	1995	270	1326	Science	HCAPLUS
Xie, Q	1993	177	1779	J Exp Med	HCAPLUS

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L98 ANSWER 1 OF 1 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN **2000418667** EMBASE
TI Protective effect of S-nitrosylated .**alpha.1-protease inhibitor** on hepatic ischemia-reperfusion injury.
AU Ikebe N.; Akaike T.; Miyamoto Y.; Hayashida K.; Yoshitake J.; Ogawa M.; Maeda H.
CS H. Maeda, Department of Microbiology, Kumamoto Univ. School of Medicine, 2-2-1 Honjo, Kumamoto 860-0811, Japan. msmaedah@gpo.kumamoto-u.ac.jp
SO Journal of Pharmacology and Experimental Therapeutics, (2000) Vol. 295, No. 3, pp. 904-911.
Refs: 40
ISSN: 0022-3565 CODEN: JPETAB
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20001221
Last Updated on STN: 20001221
AB S-Nitrosylated compounds (nitrosothiols; RS-NOs) function as nitric oxide (NO) reservoirs and preserve the antioxidant activities of NO. We found remarkable cytoprotection by an S-nitrosylated protease **inhibitor** from human plasma, S-nitroso-.**alpha.1-protease inhibitor** (S-NO-α1-PI) that possesses a completely nitrosylated SH group, in hepatic ischemia-reperfusion injuries in rats. Liver ischemia was induced in rats by occluding both the portal vein and hepatic artery for 30 min and was followed by reperfusion. S-NO-α1-PI and control compounds such as native α1-PI, an NO synthase (NOS) **inhibitor**, and standard RS-NOs were given via the portal vein just after reperfusion was initiated. Liver injury was evaluated by measuring the extracellular release of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase). Infiltration of neutrophils and induction of apoptosis and heme oxygenase-1 (HO-1) in the liver were also examined. Maximal liver injury occurred at 3 h after reperfusion and then decreased gradually. Not only did S-NO-α1-PI treatment (0.1 μmol; 5.3 mg/rat) greatly reduce elevation of liver enzymes in plasma, as well as

neutrophil accumulation and apoptotic change in liver, it also improved the impaired hepatic blood flow as assessed by laser Doppler flowmetry and potentiated the induction of HO-1 in the liver. Although native α1-PI moderately reduced liver injury, low molecular weight RS-NOs such as S-nitroso-glutathione and S-nitroso-N-acetyl penicillamine produced no obvious protective effect. An NOS **inhibitor** exacerbated the hepatic ischemia-reperfusion injuries. These results suggest that S-NO-α1-PI exerts a potent cytoprotective effect on ischemia-reperfusion liver injury by maintaining tissue blood flow, inducing HO-1, and suppressing neutrophil-induced liver damage and apoptosis.

CT Medical Descriptors:
*liver ischemia
*reperfusion injury
*liver protection
liver injury
apoptosis
neutrophil
tissue blood flow
nonhuman
rat
animal experiment
animal model
controlled study
animal tissue
article
priority journal
Drug Descriptors:
***alpha 1 antitrypsin: DV, drug development**
***alpha 1 antitrypsin: PD, pharmacology**
s nitrosoglutathione: DV, drug development
s nitrosoglutathione: PD, pharmacology
n acetyl s nitrosopenicillamine: DV, drug development
n acetyl s nitrosopenicillamine: PD, pharmacology
nitric oxide synthase inhibitor
heme oxygenase
thiol derivative
nitric oxide

RN (**alpha 1 antitrypsin**) **9041-92-3**; (s nitrosoglutathione) **57564-91-7**; (n acetyl s nitrosopenicillamine) **79032-48-7**; (heme oxygenase) 9059-22-7; (thiol derivative) 13940-21-1; (nitric oxide) **10102-43-9**

CO Chemo Sero Therapeutic Research Institute (Japan); Dojindo (Japan)

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FILE 'WPIX' ENTERED AT 10:39:33 ON 06 DEC 2005
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FILE LAST UPDATED: 5 DEC 2005 <20051205/UP>
MOST RECENT DERWENT UPDATE: 200578 <200578/DW>
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=> d all abeq tech abex tot

L114 ANSWER 1 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2005-272817 [28] WPIX
DNC C2005-085234
TI Method for treating bacterial infection in mammal, involves administering composition comprising substance exhibiting mammalian alpha-**antitrypsin** or serine protease inhibitor, and excipient.
DC B04 D16
IN **SHAPIRO, L**
PA (SHAP-I) SHAPIRO L; (COLS) UNIV COLORADO
CYC 108
PI WO 2005019434 A2 20050303 (200528)* EN 78 C12N000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2005106151 A1 20050519 (200534) A61K039-395
ADT WO 2005019434 A2 WO 2004-US27711 20040826; US 2005106151 A1 Provisional US 2003-497703P 20030826, US 2004-926051 20040826
PRAI US 2003-497703P 20030826; US 2004-926051 20040826
IC ICM A61K039-395; C12N000-00
ICS A61K038-48; C12N009-64
AB WO2005019434 A UPAB: 20050504
NOVELTY - Treatment of bacterial infection in a mammal involves administering a pharmaceutical composition comprising substance exhibiting mammalian **alpha 1-antitrypsin** or inhibitor of serine protease activity or a functional derivative, and excipient.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) relieving or ameliorating pain or symptoms associated with bacterial diseases or indications in mammal suffering from mycobacterial diseases or indications, which involves administering the pharmaceutical composition;
(2) treatment of mycobacterial infection in mammal and method of relieving or ameliorating pain or symptoms associated with mycobacterial diseases, which involves administering the composition;
(3) inhibition of mycobacterial infection of macrophages in mammal, which involves administering mammalian alpha -**antitrypsin** or serine protease inhibitor to the mammal susceptible to mycobacterial colonization of macrophages;

(4) preventing deficiency of functional endogenous alpha - **antitrypsin** levels in mammal susceptible to mycobacterial infection mediated by endogenous host serine protease or serine protease like activity, which involves treating the mammal with the pharmaceutical composition; and

(5) prevention of anthrax symptoms due to Bacillus anthracis, which involves administering substance exhibiting mammalian **alpha 1-antitrypsin** or serine protease inhibitor for blocking endogenous host protease cell surface processing of inactive large PA into active smaller PA molecule.

ACTIVITY - Antimicrobial; Antibacterial; Antiulcer; Antiinflammatory; Respiratory-Gen.; Antitussive; Immunosuppressive. No biological data given.

MECHANISM OF ACTION - Cytokine-Antagonist; IL-Antagonist-1; TNF-Antagonist-Alpha; IL-Antagonist-18; Nitric-oxide-Antagonist (all claimed).

Effect of **alpha 1-antitrypsin** on Mycobacterium avium complex infection was evaluated using human monocyte-derived macrophages (MDM) isolated from human peripheral blood mononuclear cells. MDM were infected with Mycobacterium avium (9141) strain and incubated for 1 hour. The supernatant was then removed and cytokine assays were performed. **Alpha 1-antitrypsin** significantly blocked infection of MDM with the strain, with a mean effect of 55%. The result concluded that **alpha 1-antitrypsin** exhibited excellent serine protease inhibition effect.

USE - For preventing and treating bacterial infection (mycobacterial infection), anthrax, cutaneous ulceration, edema, scar formation and inhalation anthrax, and anthrax symptoms such as pulmonary edema, lymphaonaphy, pleural effusion, ventirolatory compromise, cough, sweating, rigors and septic shock (claimed).

ADVANTAGE - The method enables effective inhibition of serine protease, and reduction or inhibition of pain and/or symptoms associated with bacterial indication(s) is in the order of 10-20%, 30-40%, 50-60% or 75-100% reduction and inhibition (claimed). The composition is highly effective against gram negative, gram positive and acid-fast bacilli, and enables modulation of cellular activities including macrophage activity and inhibition of toxin.

DESCRIPTION OF DRAWING(S) - The graph shows the effect of **alpha 1-antitrypsin** on Mycobacterium avium complex infection of human monocyte-derived macrophages.

Dwg.1/5

FS CPI

FA AB; GI

MC CPI: B12-M05; B14-A01; B14-C01; B14-C03; B14-D07C; B14-J05A; B14-K01B; B14-L06; B14-N17B; B14-N17F; B14-S06; D05-H

TECH UPTX: 20050504

TECHNOLOGY FOCUS - BIOLOGY - Preferred Microbes: The mycobacterium inhibited are Mycobacterium tuberculosis, M.bovis, M.leprae, M. avium, M.chelonei, M.africanum, M.marinium, M.buruli, M.fortuitum, M.haemophilum, M.intracellulare, M.kansasii, M.littorale, M.malmoense, M.marianum, M.simiae, M.szulgai, M.ulcerans, M.flavascens, M.lepraemurium, M.microti, M.paratuberculosis, M.gordonae, M.gastri, M.phlei, M.nonchromogenicum, M.smegmatis, M.terrae, M. triviale and M.vaccae. The mycobacterium comprises non-tuberculosis mycobacterium from four Runyon groups comprising group I (slow-growing photochromogens), group II (slow-growing scotochromogens), group III (slow-growing non-photochromogens), and group (IV) (rapidly-growing mycobacteria.

Preferred Component: The mammalian **alpha1-antitrypsin** or other serine protease inhibitor substance is optionally a portion of

fusion polypeptide comprising mammalian **alpha1-antitrypsin** or alpha-**antitrypsin** like activity substance and an amino acid sequence heterologous to mammalian **alpha1-antitrypsin** of serine protease activity substance.

ABEX UPTX: 20050504

ADMINISTRATION - The pharmaceutical composition is administered orally, systemically, intravenously, topically, intrathecally, nasally, through an implant or through inhalation. The mammalian **alpha1-antitrypsin** or serine inhibitor can be co-administered with anti-inflammatory compounds, immunomodulators, antimicrobial or antiviral composition. The anti-inflammatory compounds or immunomodulators are interferon, interferon derivatives comprising betaseron, beta-interferon, prostane derivatives comprising iloprost, cicaprost, glucocorticoids comprising cyclosporine A, FK-506, methoxsalene, thalidomide, sulfasalazine, azathioprine, methotrexate, lipoxygenase inhibitors comprising zileutone, MK-886, WY-50295, SC-45662, SC-41661A, BI-L-357, leukotriene antagonists, peptide derivatives comprising ACTH and analogs, soluble TNF receptors, TNF-antibodies, soluble receptors of inerleukines, other cytokines, T-cell-proteins, antibodies against receptors of interleukins, other cytokines, T-cell proteins and calcipotriols and/or their analogues (all claimed). The dosage of serine protease inhibitor is 5-2000 mg/unit dosage form/day, preferably 50-500 mg/unit dosage form/day.

L114 ANSWER 2 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-794491 [78] WPIX
CR 2004-783852 [77]; 2004-794473 [78]
DNC C2004-277250
TI Use of a composition comprising agent(s) that suppresses nitric oxide synthesis and exhibits e.g. mammalian alpha 1-**antitrypsin** activity, for treating a pathological condition e.g. stroke, AIDS, Alzheimer's disease or septic shock.
DC B05
IN SHAPIRO, L
PA (SHAP-I) SHAPIRO L
CYC 1
PI US 2004220242 A1 20041104 (200478)* 27 A61K031-4245 <--
ADT US 2004220242 A1 **US 2003-427929 20030502**
PRAI **US 2003-427929 20030502**
IC ICM A61K031-4245
AB US2004220242 A UPAB: 20041206

NOVELTY - Treating an animal suffering from a pathological condition comprises administering to the animal a composition comprising at least one agent that suppresses nitric oxide synthesis and exhibits mammalian alpha 1-**antitrypsin**, alpha 1-**antitrypsin**-like, elastase-inhibitory, or proteinase-3-inhibitory activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by inappropriate nitric oxide;

(2) a method of inhibiting nitric oxide production in a cell susceptible to producing nitric oxide;

(3) a pharmaceutical composition comprising at least one agent exhibiting mammalian alpha 1-**antitrypsin** or alpha 1-**antitrypsin**-like activity, and a free radical scavenger or an antioxidant;

(4) a method of treating ischemia reperfusion injury;

(5) a method of sparing tissue levels of alpha 1-**antitrypsin** in an animal; and

(6) a method of treating an animal suffering from a pathological

condition associated with elevated synthesis of nitric oxide.

ACTIVITY - Antiinflammatory; Respiratory-Gen.; Anti-HIV; Neuroprotective; Nootropic; Antiasthmatic; Antiarteriosclerotic; Immunosuppressive; Cardiant; Cytostatic; Cerebroprotective; Vasotropic; Hepatotropic; Auditory; Cardiovascular-Gen.; Antidiabetic; Gynecological; Analgesic; Antibacterial; Nephrotropic; Antimalarial; Gastrointestinal-Gen.; Ophthalmological; Hypotensive; Antiarthritic; Antimigraine; Osteopathic; Antiparkinsonian; Protozoacide; Antianemic; Antisickling; Antirheumatic; Dermatological. Experimental protocols are described but no biological data were given.

MECHANISM OF ACTION - None given.

USE - The methods are useful for treating pathological conditions such as acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome, age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, autoimmune myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular accident, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, 'hot-dog headache', Hirschsprung's disease, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease, inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, myocardial infarction, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, vascular disease, or their combinations.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B03-A; B03-F; B03-H; B04-C01A; B04-L05; B05-B02C; B06-A02; B06-H; B07-D03; B07-D11; B10-A17; B10-B02F; B10-E02; B14-A01A2; B14-A02B1; B14-A03; B14-A03B; B14-C03; B14-C06; B14-C09; B14-D01C; B14-E10B; B14-E10C; B14-F01B; B14-F01E; B14-F02; B14-F02B; B14-F02B1; B14-F02C; B14-F02D1; B14-F03; B14-F07; B14-G01B; B14-G02D; B14-J01; B14-J01A3; B14-J01A4; B14-J01B4; B14-J05; B14-K01; B14-K01A; B14-K01D; B14-K01F; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-N17B; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041206

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In treating an animal, the agent exhibits alpha1-**antitrypsin**-like activity or mammalian alpha1-**antitrypsin** activity. The agent is a substituted oxadiazole, thiadiazole, triazole peptoids, or their combinations. The agent is (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolin amide; (benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(trifluoromethyl)-1,2,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(methyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(dinuoromethyl)-1,2,4-oxadiazolyl)
carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide; (Benzyloxycarbonyl)-L-Valyl-N-
(1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-
Prolinamide; (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(3-methoxybenzyl)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolin amide;
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(2,6-difluorobenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-styryl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-4-Trifluoro
methylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolin
amide; (Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(trans-4-Methoxystyryl)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;
(Benzyloxycarbonyl)-L-Valyl-N-(I-(S-(5-(3-Thienylmethyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide;
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(Phenyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; and
(Benzyloxycarbonyl)-L-Valyl-N-(1-(3-(5-(3-Phenylpropyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl)-L-Prolinamide,
Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-(3-methyl-benzyl)-1,3,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide,
Benzyloxycarbonyl-L-valyl-N-(1-(2-(3-methylbenzyl)-1,3,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
Benzyloxycarbonyl-L-valyl-N-(1-(2-(5-(methyl)-1,3,4-oxadiazolyl)carbonyl)-
2-(S)- methylpropyl)-L-prolinamide; Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-
(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-
L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(4-Dimethylamino
benzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methyl-propyl)-L-prolinamide;
Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(1-napthylenyl)-1,3,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-(1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L- valyl-N-(1-(3-(5-(3,5-ditrifluoromethylbenzyl)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-methylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(biphenylmethine)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl)
carbonyl)-2-(S)-methylpropyl)-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-
(1-(3-(5-(3-phenylbenzyl)- 1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-
L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-phenoxybenzyl)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(cyclohexylmethylene)-1,2,4-
oxadiazolyl) carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-trifluoromethyldimethylmethylene
)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(1-napthylmethylene)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3-pyridylmethyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;
(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide;

(Benzyloxycarbonyl)-L-valyl-N-(1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide; 2-(5-((Benzyloxycarbonyl)amino)-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyljacetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 2-(5-((Benzytoxycarbonyl)amino)-6-oxo-2-(4-fluorophenyl)-1, 6-dihydro-1-pyrimidinyl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl)acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-methylpropyl)acetamide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-(1-(3-(5-(3-trifluoromethylbenzyl))-1,2,4-oxadiazolyl)-(S)-methylpropyl)amide; (2S,5S)-5-Amino-1,2,4,5,6,7-hexahydroazepino-(3,2,1)-indole-4-one-carbonyl-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(R,S)-2-methylpropyl)amide; BTD-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (R,S)-3-Amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)- methylpropylacetamide; (Benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; (Benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-methylpropyl)amide; Acetyl-2-L-(2,3-dihydro-1H-indole)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)amide; 3-(S)-(Benzyloxycarbonyl)amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 3-(S)-(Amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide trifluoroacetic acid salt; 3-(S)-((4-morpholino carbonyl-butanoyl)amino)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropylacetamide; 6-(4-Fluorophenyl)-e-lactam-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 2-(2-(R,S)-Phenyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4 oxadiazolyl)hydroxymethyl)-2-(S)-methylpropylacetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl oxide)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(R,S,)-methylpropyl)acetamide; (1-Benzoyl-3,8-quinazolinedione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl) carbonyl)-2-(S)-methylpropyl)acetamide; (1-Benzoyl-3,6-piperazinedione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; (1-Phenyl-3,6-piperazinedione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; ((1-Phenyl-3,6-piperazinedione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl))-2-(S)-methylpropylacetamide; 3-((Benzyloxycarbonyl)amino)-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-((Benzyloxycarbonyl)amino)-7-piperidinyl-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-(Carbomethoxyquinolin-2-one-N-(1-(2-(5-(3-methybenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-(Amino-quinolin-2-one)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 3-((4-Morpholino)aceto)amino-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 3,4-Dihydro-quinolin-2-one-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 1-Acetyl-3-(4-fluorobenzylidene) piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 1-Acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 1-Acetyl-3-((4-pyridyl)methylene)piperazine-2,5-dione-N-(1-(2-(5-(3-methyl benzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 4-(1-Benzyl-3-(R)-benzylpiperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-Benzyl-3-(S)-benzyl piperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 4-(1-Benzyl-3(R)- benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 4-(1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 4-(1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione)-N-(1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-((-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione)-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-((-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 4-(1-(4-Morpholino ethyl)3(R)-benzyl piperazine-2,5,-dione)-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R,S)-Phenyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl) acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1, 2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide; 1-Benzyl-4-(R)-benzyl-2,5-imidazo-lidinedione-N-(1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl) carbonyl)-2-(S)-methylpropyl)acetamide; and 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-(1-(3-(5-(3-trifluoromethyl benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropylacetamide, or their salts, or combinations. The animal is a human. The composition further comprises a carrier. Administering to an animal at least one agent exhibiting mammalian alpha1-**antitrypsin** or alpha1-anti-**trypsin**-like activity improves a pathological condition mediated by a pro-inflammatory cytokine, i.e. gamma-interferon, lipopolysaccharide, or their combination. Specifically prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by inappropriate nitric oxide comprises administering to the individual a composition comprising at least one agent described above exhibiting mammalian alpha1-**antitrypsin**, alpha1-**antitrypsin**-like, antielastase, or antiproteinase-3 activity. Inhibiting nitric oxide production in a cell susceptible to producing nitric oxide comprises contacting the cell with a composition comprising at least one agent exhibiting mammalian alpha1-**antitrypsin**, alpha1-**antitrypsin**-like, or serine protease inhibitor activity. The cell comprises at least one of an in vitro mammalian cell culture, an ex vivo mammalian tissue culture, or a mammalian organ. Treating ischemia reperfusion injury comprises administering at least one of alpha1-**antitrypsin**, alpha1-**antitrypsin**-like agent, antielastase, or antiproteinase-3 agent, or a serine protease inhibitor, or their combination. The method additionally comprises administering

a thrombolytic agent. It may additionally comprise using a mechanical device to reestablish blood flow. The ischemia reperfusion injury is associated with at least one of heart, brain, lung, kidneys, or liver. The alpha1-antitrypsin-like agent is a form of alpha1-antitrypsin resistant to inactivation by reactive oxygen intermediates. The mechanical device involves percutaneous transluminal coronary angioplasty or angioplasty. Sparing tissue levels of alpha1-antitrypsin in an animal comprises administering a nitric oxide synthase inhibitor. The animal is a human. The nitric oxide synthase inhibitor comprises NG-nitro-L-arginine methyl ester, NG-nitro-L arginine, NG-methyl-L-arginine, N,N'-dimethylarginine, NG-monoethyl-L-arginine acetate, NG-monomethyl-L-arginine acetate, NG-monomethyl-D-arginine, NG-monomethyl-L-homoarginine acetate, NG-nitro-D-arginine, N-nitro-D-arginine methyl ester hydrochloride, (nitro-L-arginine, L-N6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenylenciodonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinosydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, S-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or their free bases or salts. Treating an animal suffering from a pathological condition associated with elevated synthesis of nitric oxide comprises administering to an animal at least one inhibitor of proteinase-activated receptor. The method further comprises a pharmaceutical carrier. The inhibitor comprises alpha1-antitrypsin, alpha1-antitrypsin-like agents, blocking antibodies, inhibitory kinases, cDNA of inhibitory kinase, inhibitory proteases, hirudin, or their combinations. Preferred Composition: The pharmaceutical composition further comprises a pharmaceutical carrier. The antioxidant is vitamin A, vitamin E, vitamin C, cysteine, N-acetylcysteine, omega-3-unsaturated lipids, omega-6-unsaturated lipids, alpha-carotene, beta-carotene, selenium, curcumin, a Superoxide dismutase preparation, or their combinations or complexes.

ABEX UPTX: 20041206

WIDER DISCLOSURE - Disclosed are:
(a) a method of inhibiting bacterial colonization in a host; and
(b) a method of preventing a deficiency of functional endogenous alpha1-**antitrypsin** levels in patient susceptible to an infection that is mediated by endogenous host serine protease or serine protease-like activity.

ADMINISTRATION - Dosage is 1 ng-10 mg per ml of biological fluid of the animal administered once daily to about once hourly or within four hours of an ischemic event, by osmotic pump, parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, or their combinations (claimed).

EXAMPLE - No relevant example given.

L114 ANSWER 3 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-794473 [78] WPIX
CR 2004-783852 [77]; 2004-794491 [78]
DNC C2004-277232
TI Sparing tissue levels of **alpha-1-antitrypsin**

in animal for treatment of inflammatory diseases or disorders, or hypotension, comprises administering **nitric oxide synthase** inhibitor.

DC B05
IN **SHAPIRO, L**
PA (SHAP-I) SHAPIRO L
CYC 1
PI US 2004220113 A1 20041104 (200478)* 22 A61K038-04 <--
ADT US 2004220113 A1 **Div ex US 2003-427929 20030502, US 2003-669250 20030925**
PRAI **US 2003-427929 20030502; US 2003-669250 20030925**
IC ICM A61K038-04
ICS A61K031-4245

AB US2004220113 A UPAB: 20041206
NOVELTY - Sparing tissue levels of **alpha 1-antitrypsin** in animal, comprises administering **nitric oxide synthase** inhibitor.

ACTIVITY - Vasotropic; Hypertensive; Respiratory-Gen.; Anti-HIV; Neuroprotective; Nootropic; Antiasthamatic; Antiarteriosclerotic; Immunosuppressive; Cardiant; Cytostatic; Antiinflammatory; Cerebroprotective; Cardiovascular-Gen.; Antidiabetic; Analgesic; Gynecological; Antibacterial; Nephrotropic; Ophthalmological; Gastrointestinal-Gen.; Hypotensive; Antiulcer; Hepatotropic; Antimigraine; Antiarthritic; Osteopathic; Antiparkinsonian; Protozoacide; Antianemic; Antisickling; Antirheumatic; Dermatological.

MECHANISM OF ACTION - Serine protease inhibitor; Antagonist.

USE - For sparing tissue levels of **alpha 1-antitrypsin** in animal, e.g. human, and for treatment of inflammatory diseases or disorders, or hypotension, acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, 'hotdog headache', Hirschprung's disease, HIV infection, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint disease, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, or vascular disease.

ADVANTAGE - The method provides for treatment of diseases dependent on the action of NO and proteases. The serine protease inhibitors exhibit high activity at low concentrations.

Dwg.0/7

FS CPI

FA AB; DCN
MC CPI: B02-T; B04-B04D2; B06-D05; B06-F03; B07-D03; B07-D12; B07-D13; B10-A03; B10-A05; B10-A13A; B10-A17; B10-B01B; B14-A02B1; B14-A03; B14-A03B; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C; B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F07; B14-F08; B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; B14-L06; B14-N01; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08
TECH UPTX: 20041206
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The nitric oxide (NO) synthase inhibitor comprises N-G-nitro-L-arginine methyl ester, N-G-nitro-L-arginine N,N'-dimethylarginine, N-G-monoethyl-L-arginine acetate, N-G-monomethyl-L-arginine acetate, N-G-monomethyl-D-arginine, N-G-monomethyl-L-homoarginine acetate, N-G-nitro-D-arginine, N-G-nitro-D-arginine methyl ester gydrochloride, omega-nitro-arginine, L-N6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenyleneiudonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N-5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinosydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, A-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or their free bases or salts.
ABEX UPTX: 20041206
ADMINISTRATION - Doses are administered at 0.01-20 mg/ml biologic fluid of treated patient, by injection, continuous intravenous infusion, transdermally, or orally.

L114 ANSWER 4 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-783852 [77] WPIX
CR 2004-794473 [78]; 2004-794491 [78]
DNC C2004-274208
TI Use of alpha-1-**antitrypsin**, alpha-1-**antitrypsin**-like agent, antielastase, antiproteinase-3 agent and/or serine protease inhibitor for the treatment of ischemia reperfusion injury.
DC B05
IN SHAPIRO, L
PA (SHAP-I) SHAPIRO L
CYC 1
PI US 2004220239 A1 20041104 (200477)* 22 A61K031-433 <--
ADT US 2004220239 A1 **Div ex US 2003-427929 20030502, US 2003-669251 20030925**
PRAI **US 2003-427929 20030502; US 2003-669251 20030925**
IC ICM A61K031-433
ICS A61K031-4245
AB US2004220239 A UPAB: 20041206
NOVELTY - Treatment of ischemia reperfusion injury involves administration of at least one of alpha 1-**antitrypsin**, alpha 1-**antitrypsin**-like agent, antielastase, antiproteinase-3 agent and/or serine protease inhibitor.
ACTIVITY - Vasotropic; Cerebroprotective; Nephrotropic; Nootropic; Neuroprotective; Respiratory-Gen.; Antiinflammatory; Hepatotropic; Anti-HIV; Virucide; Immunosuppressive; Antidiabetic; Auditory; Cardiant; Gynecological; Analgesic; Antibacterial; Ophthalmological; Antimalarial; Gastrointestinal-Gen.; Osteopathic; Antiasthmatic; Antiarteriosclerotic;

Protozoacide; Dermatological; Cytostatic; Hypotensive; Antiulcer; Antimigraine; Antianemic; Antisickling; Antirheumatic; Tranquilizer; Vulnerary; Antiarthritic; Antiparkinsonian.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor. The efficacy of alpha 1-**antitrypsin** (Ia) to inhibit nitric oxide synthesis was evaluated in macrophages. RAW 264.5 cell monolayers of macrophages were treated with (Ia) (0.1 - 3 mg/ml), followed by costimulation with interferon- gamma (10 U/ml) and lipopolysaccharide (1 ng/ml) for 18 hours. After incubation aliquots of supernatant were combined with Greiss reagent and incubated at room temperature for 10 minutes and then nitric oxide concentration was measured colorimetrically. The cell layers were treated with costimulants without (Ia) as control. The produced nitric oxide (nmol of NO2/106 cells) was found to be 1, 2, 4.5 and 8 in the cell supernatant treated with 3, 1 and 0.1 mg/ml of (Ia) and control respectively.

USE - For the treatment of ischemia reperfusion injury associated with heart, brain, lung, kidneys or liver (claimed). Also for the treatment of acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, cytomegalovirus infection, Herpes simplex infection, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, heart failure, heat stress, gastritis, hypertension, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint diseases, liver cirrhosis, liver disease, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, preeclampsia, primary ciliary dyskinesia, protozoan infections, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, and vascular disease.

ADVANTAGE - The method is safe and effective for amelioration of many diseases related to nitric oxide-caused damage. The therapeutic agents used exhibit significant potential as nitric oxide synthesis inhibitor, and high activity at relatively low concentration.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B04-M01; B04-N02; B04-N04A; B07-D03; B07-E04; B14-A02A3; B14-A03; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C; B14-E08; B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F05; B14-F07; B14-F08; B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; B14-N02; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041203

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves administration of a thrombolytic agent; and using a mechanical device to reestablish blood flow. The mechanical device involves angioplasty or percutaneous transluminal coronary angioplasty. Preferred Component: The alpha1-**antitrypsin**-like agent is a form of alpha1-**antitrypsin** resistant to inactivation by reactive oxygen intermediates.

ABEX UPTX: 20041203

ADMINISTRATION - Dosage of the compounds is 0.01 - 20 mg/ml of biological

fluid of treated patient. Administration is by oral, topical, transdermal, parenteral (including subcutaneous, intravenous, intraarterial, intranasal, intraperitoneal, intramuscular), transbronchial, transalveolar, or rectal route.

EXAMPLE - No relevant example given.

L114 ANSWER 5 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-098593 [10] WPIX
DNC C2004-040683
TI Treatment of congenital protein deficiency by administering endothelial progenitor cells that comprise gene encoding functional form of protein responsible, for congenital deficiency at stage of subject's life.
DC B04 D16
IN SANDS, M S; YOUNG, P P
PA (UNIW) UNIV WASHINGTON
CYC 1
PI US 2004009158 A1 20040115 (200410)* 23 A61K048-00
ADT US 2004009158 A1 Provisional US 2002-395004P 20020711, US 2003-616821 20030710
PRAI US 2002-395004P 20020711; US 2003-616821 20030710
IC ICM A61K048-00
AB US2004009158 A UPAB: 20040210
NOVELTY - A congenital protein deficiency is treated by administering endothelial progenitor cells that comprise a gene encoding a functional form of the protein responsible, for the congenital deficiency at a stage of the subject's life, at which non-pathologic vasculogenesis occurs.

ACTIVITY - Hemostatic; Thrombolytic; Cardiovascular-Gen; CNS-Gen; Nephrotropic.

MECHANISM OF ACTION - None given.

USE - The invention is for treatment of congenital protein deficiency in human. Congenital protein deficiency comprises a blood protein disorder or lysosomal storage disease. The blood protein disorder comprises hemophilia A, hemophilia B, von willebran disease, **alpha 1-antitrypsin** deficiency, or antithrombin III deficiency. The lysosomal storage disease comprises gaucher's disease, mucopolysaccharidosis type VII (MPS VII), fabry disease, MPS I, niemann-pick disease, farber disease, or pompe disease. (all claimed)

ADVANTAGE - Even though a deficient protein may be expressed in cells other than endothelial cells in the absence of the congenital deficiency, expression and secretion of the functional form of the deficient protein by endothelial cells alone can provide a sufficient amount of the functional protein to cure, ameliorate, or inhibit the congenital deficiency. GUSB-deficient newborn mice received 1.25 ng or 0.4 ng of rh VEGF164 (RTM) with or without bone marrow cells at day 1 of birth, and a repeat administration of an equivalent dose of rh VEGF164 alone IV on day 3 after birth. Enzyme activity was increased in tissues, including the heart and liver, when bone marrow cells were administered with vascular endothelial growth factor (VEGF). The increased levels of donor cell in VEGF-treated recipients persisted even after 2 months. Quantitative analysis of the spleen suggested no increased donor hematopoietic engraftment, in the presence of VEGF, when compared to recipients of bone marrow cells alone.

Dwg.0/5
FS CPI
FA AB; DCN
MC CPI: B01-B01; B01-B02; B02-C01; B04-B04D2; B04-E03F; B04-F0100E; B04-H06; B04-N06; B05-B01J; B06-D09; B14-F01; B14-F02; B14-F03; B14-F04; B14-F06; B14-F08; B14-G02; B14-J01; B14-N12; D05-H14
TECH UPTX: 20040210

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The subject is treated pre- or post-natally. The method comprises administration of an immunosuppressive drug consisting of cyclosporine A, prednisone, methyl prednisolone, azathioprine, cyclophosphamide, antilymphocyte globulin, or antithymocyte globulin. It comprises administration of a dose of radiation prior to the administration of endothelial progenitor cells. It comprises administration of an endothelial cell mitogen consisting of vascular endothelial growth factor (VEGF), acidic and basic fibroblast growth factors, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, erythropoietin, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

Preferred Component: The endothelial progenitor cells comprise autologous endothelial progenitor cells, which are modified ex vivo prior to its administration to the subject, where the modification of the cells comprises introducing into the cells a gene encoding a functional form of the protein responsible for the congenital deficiency. It comprise heterologous endothelial progenitor cells, which are modified ex vivo prior to its administration to the subject, where the modification of the cells comprises introducing into the cells a gene encoding a functional form of the protein responsible for the congenital deficiency, where the deficient protein is not expressed by endothelial cells of other subjects not suffering from the congenital protein deficiency.

ABEX UPTX: 20040210

ADMINISTRATION - The endothelial progenitor cells administered to the patient is between 106-1018, preferably 109-1012.

L114 ANSWER 6 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-748649 [70] WPIX
DNC C2003-205316
TI New conjugate, useful for treatment or diagnosis of vascular disease, comprises CD13-aminopeptidase N homing molecule and active agent.
DC B04 B05 D16
IN DEMUINCK, E D; **SHAPIRO, L H**; DE MUINCK, E D
PA (CARD-N) CARDIOVASCULAR RES INST MAASTRICHT; (SJUD-N) ST JUDES CHILDRENS RES HOSPITAL; (SJUD-N) ST JUDE CHILDREN'S RES HOSPITAL
CYC 104
PI WO 2003078569 A2 20030925 (200370)* EN 43 C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
EP 1346729 A1 20030924 (200373) EN A61K047-48
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2003225405 A1 20030929 (200432) C12N000-00
ADT WO 2003078569 A2 WO 2003-NL207 20030319; EP 1346729 A1 EP 2002-76146 20020319; AU 2003225405 A1 AU 2003-225405 20030319
FDT AU 2003225405 A1 Based on WO 2003078569
PRAI US 2002-365190P 20020319; EP 2002-76146 20020319
IC ICM A61K047-48; C12N000-00
AB WO2003078569 A UPAB: 20031030

NOVELTY - A conjugate comprising a CD13/APN (aminopeptidase N) homing molecule (I) conjugated to an agent (II) for treatment or diagnosis of a vascular disease, is new.

ACTIVITY - Cardiant; Vasotropic; Antiarteriosclerotic; Vulnerary.
Test methods are described but no results are given.
MECHANISM OF ACTION - None given.
USE - Compositions of the conjugate are useful for treating ischemic mycocardium or an ischemic extremity, or improving recovery after percutaneous coronary or peripheral intervention. The conjugate is especially useful for treating a chronic ischemic myocardium, especially one resulting from a myocardial infarction. Treatment results in:
(a) improved perfusion of the ischemic myocardium;
(b) a reduction in size of the ischemic zone;
(c) a reduction in the amount of myocardial tissue loss;
(d) prevention of further tissue loss; or
(e) a combination of the above effects.
The conjugate is useful for treating a chronic ischemic extremity, especially one resulting from an arterial occlusion and the effects are similar to those listed above. The conjugate is useful for accelerating wound healing after percutaneous coronary or peripheral intervention, or for preventing neointimal thickening of treated arterial segments. The conjugate is useful for treating a rupture prone atherosclerotic plaque. The conjugate is useful in a diagnostic method comprising vascular imaging, especially for diagnosing the presence of (rupture prone) atherosclerotic plaques. The imaging is preferably of the (angiogenic) vasculature of atherosclerotic plaques. The imaging method is a method for diagnosing the status, size, risk of rupture, or the development of the atherosclerotic plaque in time, especially for monitoring response to a therapeutic treatment. The imaging is especially performed in a subject that has suffered a myocardial infarction, and the imaging is of the ischemic border zone at the perimeter of the infarcted myocardium. The imaging may also be of myocardial vasculature in a subject suffering from chronic myocardial ischemia, or of the vasculature of the extremities in a subject that has suffered an acute or chronic arterial occlusion (all claimed).
Dwg.0/2

FS CPI
FA AB; DCN
MC CPI: B04-C01; B04-E08; B04-G01; B04-J01; B04-N08; B11-C08A; B11-C09; B12-K04A2; B12-K04C; B14-F02D2; B14-F02F; B14-N17B; B14-S03; D05-H09; D05-H11
TECH UPTX: 20031030

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Materials: (I) is preferably a CD13/APN homing peptide, and (II) is an angiogenesis-promoting molecule, especially a growth factor selected from vascular endothelial growth factor (VEGF), placental growth factor (PIGF), basic fibroblast growth factor (bFGF), macrophage-derived peptides PR39 and PR11, CD154, the extracellular domain of CD154 in soluble form, platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), and scatter factor. The growth factor is especially a heterodimer of VEGF and PIGF. The conjugate may comprise the amino acid sequence of a CD13/APN homing peptide and an angiogenic growth factor as a single polypeptide chain.
(II) may be a molecule that stabilizes or reduces atherosclerotic plaques, and is especially an antiangiogenic agent, a hydroxymethylglutarate CoA reductase inhibitor, an expression vector for inducible or endothelial **nitric oxide synthase**, an antioxidant, 5-methyltetrahydrofolate or a CD154 antibody. The agent that stabilizes or reduces atherosclerotic plaques is especially endostatin, bestatin, TNP-470, angistatin, thrombospondin 1 or 2, or the kringle 5 domain from plasminogen. The agent may also be suramin, a 3-(3-substituted -1,2,4-thiadiazol-5-yl)pyridazine, thalidomide, a cytocholasin, isoindolinone, or a derivative.
The agent may be an imaging agent, especially one detectable by magnetic

resonance, ultrasound, or both.
Preparation: (I) and (II) are conjugated by usual chemical methods, e.g. using a carbodiimide, or where (II) is a peptide they are expressed together as a recombinant fusion protein.

ABEX UPTX: 20031030
ADMINISTRATION - Compositions of the conjugate are administered intravenously or intra-arterially by infusion or injection. No dosage given.

EXAMPLE - No relevant examples are given.

L114 ANSWER 7 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-611339 [58] WPIX
CR 2000-572151 [50]; 2000-587294 [50]; 2000-594139 [50]
DNC C2000-182850
TI Treating herpes virus infection and associated disease by administering **alpha1-antitrypsin** or compound with similar activity.
DC B05 C03 D16
IN **SHAPIRO, L**
PA (UYTE-N) UNIV TECHNOLOGY CORP
CYC 87
PI WO 2000051625 A1 20000908 (200058)* EN 86 A61K038-08
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000038640 A 20000921 (200065) A61K038-08
ADT WO 2000051625 A1 WO 2000-US5557 20000303; AU 2000038640 A AU 2000-38640 20000303
FDT AU 2000038640 A Based on WO 2000051625
PRAI US 1999-153942P 19990915; US 1999-123167P 19990305
IC ICM A61K038-08
ICS A61K038-57; A61P031-22
AB WO 200051625 A UPAB: 20001214
NOVELTY - Treating herpes virus (HV) infection and associated disease comprises administering an agent (I) with mammalian **alpha 1-antitrypsin** (aaT) or aaT-like activity.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising a peptide of formula (A) or its salts.
Nt = amino acid (aa), including C, acetyl, succinyl or is absent;
X1 = aa, including F or A;
X2 = aa, including C, V, L, M, I, A, C or S;
X3 = aa, including F, A, V, M, L, I, Y or C;
X4 = aa, including L, A, F, I, V, C, G or S;
X5 = aa, including M, A, I, L, V, F or G;
Ct = aa, including C, an amide or ester, or is absent.
aa Has L- or D-configuration.
ACTIVITY - Antiviral; cytostatic; neuroprotective; antipyretic; dermatological; antiulcer; hepatotropic; antidiarrheal; antibacterial.
Herpes simplex-1 or -2 was used to infect semi-continuous human lung fibroblasts in the presence or absence of aaT, then virus removed and the cells cultured. The amount of virus produced was determined by enzyme-linked immunosorbent assay and the measured optical density was 0.8 in the absence of aaT but only 0.5 when aaT was present at 3 mg/ml.
MECHANISM OF ACTION - Serine protease inhibitor; **trypsin** inhibitor.
USE - Used for treating HV infection mediated by an endogenous serine

protease or SP-like activity and inhibiting the spread or onset of viral infection mediated by endogenous SP or SP-like activity, and for preventing sexually transmitted diseases (all claimed) by intravaginal or intrarectal administration of (I) or its derivatives that can inhibit caspase, proteinase-3, cathepsin G and/or elastase. (I) Is used for treating infection by herpes simplex-1 and -2 viruses, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, herpes zoster and human herpes viruses 5, 6 and/or 8. (I) Is used for treating malaise, fever, chills, rhinitis, diarrhea, atopic eczema, encephalitis, keratoconjunctivitis, pharyngitis, gingivostomatitis, hepatitis, recurrent orofacial mucocutaneous lesions or herpes labialis, chicken pox skin sores, erythema multiforme, idiopathic burning mouth, aphthous ulceration, Behcet's syndrome, mononucleosis, Burkitt's lymphoma and other tumors and neuropathies. Particularly, (I) is used against HV infections of the mucosa (oral, middle ear, gastrointestinal, urogenital, airway/lung, eye, peritoneal membranes etc.), including sexually transmitted diseases. Treatment with (I) is also used to restore defective levels of functional endogenous aaT and to prevent development of such a condition, in treating infections by viruses other than herpes, to prevent bacterial colonization concurrent with viral infection and also very generally wherever inhibition of serine protease activity is required, e.g. in medicine, biology, agriculture or microbial fermentation.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B04-C01A; B07-D13; B07-E04; B07-F03; B10-A08; B10-A10; B10-A17; B14-A01; B14-A02A3; B14-C04; B14-D07C; B14-E02; B14-E08; B14-H01; B14-N03; B14-N04; B14-N06B; B14-N12; B14-N16; B14-N17; C04-C01A; C07-D13; C07-E04; C07-F03; C10-A08; C10-A10; C10-A17; C14-A01; C14-A02A3; C14-C04; C14-D07C; C14-E02; C14-E08; C14-H01; C14-N03; C14-N04; C14-N06B; C14-N12; C14-N16; C14-N17; D05-H17A6; D05-H17B6

TECH UPTX: 20001114

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: (I) Comprises:
(i) aaT, particularly isolated from wild-type, mutant or transgenic mammalian sources;
(ii) a peptoid substituted by oxadiazole, thiadiazole or triazole, phenylene dialkanoate, tetrazole, guanidinobenzoic acid, phenylsulfonylamide, sulfide, sulfoxide, sulfone, amidine, amidinophenol or their derivatives, or
(iii) peptides (A).

ABEX UPTX: 20001114

SPECIFIC COMPOUNDS - About 90 compounds are used e.g: (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (Ia).
27 Peptides (A) are used e.g. Phe-Val-Phe-Leu-Met.

ADMINISTRATION - (I) is administered at 1 mug to 100 mg/kg/day, preferably 10-25 mg/kg/day, systemically or topically. When administered topically, (I) may be combined with an anesthetic, analgesic and/or antibiotic.

L114 ANSWER 8 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2000-594139 [56] WPIX

CR 2000-572151 [50]; 2000-587294 [50]; 2000-611339 [50]

DNC C2000-177373

TI Treating excessive apoptosis, e.g. cancer or neurodegeneration, by administering inhibitor of serine protease, e.g. **alpha1-antitrypsin** or analog.

DC B02 B03

IN **SHAPIRO, L**

PA (UYTE-N) UNIV TECHNOLOGY CORP

CYC 87
PI WO 2000051624 A2 20000908 (200056)* EN 29 A61K038-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000037314 A 20000921 (200065) A61K038-00
ADT WO 2000051624 A2 WO 2000-US6069 20000303; AU 2000037314 A AU 2000-37314 20000303
FDT AU 2000037314 A Based on WO 2000051624
PRAI US 1999-123167P 19990305
IC ICM A61K038-00
AB WO 200051624 A UPAB: 20001214
NOVELTY - Treatment of diseases associated with excessive apoptosis comprises administering at least one inhibitor (I) of serine protease (SP).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) prophylactic treatment of subjects at risk of developing an apoptotic disease by administering at least one agent (Ia) with mammalian **alpha 1-antitrypsin** (aaT) or aaT-like activity;

(2) inhibiting apoptosis in vitro in mammalian cells, ex vivo in mammalian tissue cultures and organs by administering (I);

(3) inhibiting apoptosis by treating cells with (I); and

(4) sustaining aaT activity in blood by administering (i) aaT to replace inactivated aaT or (ii) a variant of aaT, or a synthetic aaT, that is not inactivated by free radicals.

ACTIVITY - Cytostatic; immunosuppressive; antiarthritic; antiinflammatory; antidiabetic; neuroprotective; antibacterial; vasotropic; hepatotropic; anti-HIV; cerebroprotective.

MECHANISM OF ACTION - Serine protease inhibitor; oxygen free radical inhibitor; oxygen free radical formation inhibitor.

Rat brain cerebral granule cells were incubated for 10 hours in (i) conditioned medium with serum; (ii) Eagle basic medium (EBM) without serum or (iii) EBM containing 60 micro M of the peptoid (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4- oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I'). The cells were then fixed, stained and analyzed for apoptosis. The proportion of apoptotic cells was less than 5% in (i), about 45% in (ii) and about 8% in (iii).

USE - The method is used to treat or prevent cancer; autoimmune diseases (e.g. arthritis, multiple sclerosis or diabetes); neurodegeneration; sepsis; ischemic reperfusion injury; toxin-mediated liver disease; acquired immune deficiency syndrome (AIDS), or particularly myocardial infarction and stroke. (I) may also be used to inhibit apoptosis in vivo or ex vivo, e.g. in cell cultures, tissues and organs and to sustain endogenous levels of aaT.

ADVANTAGE - The treatment is effective against apoptosis however this is induced in a wide range of organs.

Dwg.0/2
FS CPI
FA AB; DCN
MC CPI: B07-D03; B07-E04; B14-A02; B14-C09; B14-F01; B14-F01E; B14-F02; B14-F02D1; B14-G01B; B14-G02D; B14-H01; B14-N12; B14-N16; B14-S01; B14-S06
TECH UPTX: 20001106
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Process: (I) is at least one of aaT or its variants, an aaT-like agent, anticathepsin G, antitryptase TL-2, antifactor Xa, anti-elastase and/or antiproteinase-3

agents (especially a substituted oxadiazole, thiadiazole or triazole peptoid, optionally modified by esterification, acetylation or amidation). Treatment may include administration of a free radical scavenger or inhibitor (II) and may be monitored, particularly by taking biopsies. Preferred Materials: In (4), variants of aaT particularly have one of the residues Val, Ile, Leu, Phe, Tyr or Trp at position 358.

ABEX UPTX: 20001106

SPECIFIC COMPOUNDS - Use of about 90 (I) is claimed, e.g. (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I')

ADMINISTRATION - Dosage of (I) is 0.3-7 g/kg, to provide 10 pM to 2 mM (I) in biological fluid, especially blood. Administration is oral, vaginal, rectal, nasal, buccal, intravenous, intramuscular, subcutaneous, intrathecal, epidural, transdermal, intracerebroventricular and/or by osmotic pump (all claimed).

L114 ANSWER 9 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-587294 [55] WPIX
CR 2000-572151 [53]; 2000-594139 [56]; 2000-611339 [58]
DNC C2000-175124
TI Treating diseases mediated by serine protease, particularly viral infection and cancer, by administering **alpha1-antitrypsin** or its functional equivalent.
DC B05
IN **SHAPIRO, L**
PA (UYTE-N) UNIV TECHNOLOGY CORP
CYC 88
PI WO 2000052034 A2 20000908 (200055)* EN 86 C07K007-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000037191 A 20000921 (200065) C07K007-00
US 6849605 B1 20050201 (200511) C07K005-06
ADT WO 2000052034 A2 WO 2000-US5558 20000303; AU 2000037191 A AU 2000-37191 20000303; US 6849605 B1 Provisional US 1999-123167P 19990305, Provisional US 1999-137795P 19990603, US 2000-518098 20000303
FDT AU 2000037191 A Based on WO 2000052034
PRAI US 1999-137795P 19990603; US 1999-123167P 19990305; US 2000-518098 20000303
IC ICM C07K005-06; C07K007-00
AB WO 200052034 A UPAB: 20050217

NOVELTY - A viral infection, or any other pathological condition, that is mediated by an endogenous host serine protease (SP), or SP-like activity, is treated by administering an agent (I) with mammalian **alpha 1-antitrypsin** (aaT) or aaT-like activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) inhibiting, in mammals, spread or onset of viral infection by administering (I);

(b) method for treating a patient with deficiency of functional endogenous aaT, and susceptible to virus infection, by administering (I);

(c) method for treating a viral infection mediated at least in part by SP, by administering (I);

(d) method for inhibiting human immune deficiency virus (HIV) replication in a subject by administering a compound (II) with binding affinity to a ligand-binding domain of an SEC (serpin-enzyme complex) receptor;

(e) method for preventing or inhibiting entry of viral nucleic acid into a host cell, or release of virions from such a cell, by administering (I);

(f) preventing a deficiency of functional endogenous aaT in a mammal susceptible to virus infection by administering (I);

(g) pharmaceutical composition containing (I) and a carrier; and

(h) method for treating HIV infection by administering a combination of at least one (I) plus an inhibitor (III) of HIV reverse transcriptase (RT) and/or protease.

ACTIVITY - Antiviral; anticancer.

The U1 cell line, containing two copies of the HIV-1 proviral integrated into its genome, was exposed to 0.5 nM interleukin(IL)-18 and then after 48 hours was expressing a mean of 6235 pg/ml of the p24 antigen, compared with 41.3 pg/ml without exposure to IL-18. When the cells were incubated for 1 hour with 3 mg/ml of aaT before exposure to IL-18, the mean p24 production was reduced to 179 pg/ml.

MECHANISM OF ACTION - Inhibition of SP activity that is involved in viral activation and infection, resulting in inhibition of entry of viral nucleic acid into cells and/or release of assembled virions from cells.

USE - (I) are especially used to treat or prevent retroviral, specifically HIV (human immune deficiency virus) infection, including treatment of pregnant women and subjects exposed to (or at risk of exposure to) HIV. They may also be used to treat a very wide range of cancers, where these are induced by a virus (e.g. solid tumors, myeloma, lymphoma or leukemia). Also, (I) may be used to restore endogenous layers of aaT, where the deficiency is acquired or congenital, or very generally, to inhibit SP activity in any situation, e.g. in medicine, biology, agriculture or microbial fermentation.

ADVANTAGE - (I) have relatively high activity at low concentrations and show a synergistic effect when formulated with known anti-HIV agents.

Dwg.0/14

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B07-D03; B07-E04; B14-A02; B14-A02B1; B14-H01

TECH UPTX: 20001102

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) is aaT, isolated from human plasma, a transgenic mammal, or a culture of wild-type, mutant or transformed cells, and has inhibitory activity against HIV production induced by at least one of interleukin-6 or -18, tumor necrosis factor or lipopolysaccharide. Alternatively (I) is (i) a peptoid (Ia) that includes an oxadiazole, thiadiazole or triazole residue; (ii) a peptide that binds to the SEC receptor; (iii) a peptide (Ib) containing at least 5 amino acids from the C-terminal region of mammalian aaT, or its analogs or homologs; (iv) heterocyclic compounds; (v) cyclic (di)keto compounds; (vi) tripeptoid analogs; (f) proline analogs or (g) a compound that inhibits proteinase-3, elastase, eglin, thrombin, cathepsin G, **chymotrypsin**, plasminogen activator or plasmin. Particularly (Ib) have formula I-A-B-C-D-E-F-G-H-II

I = Cys or is absent;
A = Ala, Gly, Val or is absent;
B = Ala, Gly, Val, Ser or is absent;
C = Ser, Thr or is absent;
D = Ser, Thr, Asn, Glu, Arg, Ile, Leu or is absent;
E = Ser, Thr, Asp or is absent;
F = Thr, Ser, Asn, Gln, Lys, Trp or is absent;
G = Tyr or is absent;
H = Thr, Gly, Met, Met(O), Cys, Thr or Gly;
II = Cys, optionally substituted amide or ester, or is absent, provided that at least 4 amino acids are present.

(III) is e.g. retrovir, combivir, viramine etc. (12 listed) as RT

inhibitors or e.g. fortovase, norvir or angenerase (9 listed) as protease inhibitors.

ABEX UPTX: 20001102

SPECIFIC COMPOUNDS - (I) is aaT; any of about 90 peptoids specified, e.g. (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I'); or any of 18 specified aaT-derived peptides, e.g. FVFLM.

ADMINISTRATION - (I) are administered to provide 1 ng-30 mg, particularly 0.1-10 mg/ml of body fluid in the subject, e.g. topically (including incorporation into condoms or intravaginal devices), by injection or orally. Unit doses contain 5-2000 (particularly 50-500) mg (I).

L114 ANSWER 10 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-572151 [53] WPIX
CR 2000-587294 [55]; 2000-594139 [56]; 2000-611339 [58]
DNC C2000-170609
TI Treating disease e.g. autoimmune disease and hypertension by administering agent which inhibits nitric oxide synthesis and e.g. **alpha1-antitrypsin**.
DC B05 C03 D16
IN **SHAPIRO, L**
PA (UYTE-N) UNIV TECHNOLOGY CORP
CYC 88
PI WO 2000051623 A2 20000908 (200053)* EN 49 A61K038-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000035115 A 20000921 (200065) A61K038-00
US 6489308 B1 20021203 (200301) A61K031-70
ADT WO 2000051623 A2 WO 2000-US5556 20000303; AU 2000035115 A AU 2000-35115 20000303; US 6489308 B1 Provisional US 1999-123167P 19990305, Provisional US 1999-156523P 19990929, US 2000-518097 20000303
FDT AU 2000035115 A Based on WO 2000051623
PRAI US 1999-156523P 19990929; US 1999-123167P 19990305; US 2000-518097 20000303
IC ICM A61K031-70; A61K038-00
ICS A61K031-16; A61K031-35; A61K031-40
AB WO 200051623 A UPAB: 20030101
NOVELTY - Diseases are treated by administering at least one agent (I) that:

(1) suppresses nitric oxide (NO) synthesis and

(2) has mammalian **alpha 1-antitrypsin** (aaT), aaT-like, elastase-inhibiting or proteinase-3-inhibiting activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(I) treating subjects at risk of diseases produced, at least partly, by inappropriate NO, by administering at least one agent with aaT, aaT-like, elastase-inhibiting or proteinase-3-inhibiting activity;

(II) inhibiting NO production in cells by treatment with at least one agent having aaT, aaT-like or serine protease inhibiting activity;

(III) a composition comprising at least one agent having aaT or aaT-like activity and a free radical scavenger or antioxidant;

(IV) treating ischemic reperfusion injury by administering at least one of aaT, aaT-like agent, antielastase or antiproteinase-3 agent or serine protease (SP) inhibitor;

(V) sparing tissue levels of aaT by administering an inhibitor of NO

synthase and

(VI) treating disease associated with high levels of NO synthesis by administering at least one inhibitor of a proteinase-activated receptor.

ACTIVITY - Antiinflammatory; neuroprotective; immunostimulant; antiasthmatic; antiarteriosclerotic; immunosuppressant; cytostatic; Cerebroprotective; hepatotropic; ophthalmological; cardiant; antimalarial; gastrointestinal; analgesic; hypotensive; antiarthritic; antidiabetic; antihypertensive; antitumor; protozoacide; antiviral; respiratory; antianemic; dermatological.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor; serine protease inhibitor; **trypsin** inhibitor; elastase inhibitor; proteinase-3 inhibitor.

(Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I') was tested for inhibition of NO synthesis, produced by inducible NO synthase after induction with 0.5 ng/ml lipopolysaccharide and 10 units/ml of interferon-gamma , in RAW264.5 macrophages. In absence of (Ia), synthesis was 90 nmole per million cells, but in the presence of 60 mu M (Ia) it was only 10 nmole per million cells.

USE - Used in human or veterinary medicine for treating tubulointerstitial disease, acute pancreatitis, acute respiratory failure or distress syndrome, age associated memory impairment, AIDS, airway inflammation, Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, autoimmune myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular accident, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, hot dog headache, Hirschsprung's disease, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease, inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, myocardial infarction, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression and vascular disease.

ADVANTAGE - Treatment with (I) reduces NO-mediated side effects associated with treating cancer with interleukin-2 or tumor necrosis factor and prevents inactivation of endogenous aaT by peroxynitrite (derived from NO).

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B03-A; B03-F; B03-H; B04-B01B; B05-B02C; B07-D13; B07-E04; B07-F03; B10-B01B; B14-A03; B14-A03B; B14-C01; B14-C03; B14-C09; B14-D07C; B14-D08; B14-E10; B14-E10C; B14-F01B; B14-F02B; B14-F03; B14-F07; B14-G02D; B14-H01; B14-J01A3; B14-J01A4; B14-K01; B14-K01A; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08; B14-S12; C03-A; C03-F; C03-H; C04-B01B; C05-B02C; C07-D13; C07-E04; C07-F03; C10-B01B; C14-A03; C14-A03B; C14-C01; C14-C03; C14-C09; C14-D07C; C14-D08; C14-E10; C14-E10C; C14-F01B; C14-F02B; C14-F03; C14-F07; C14-G02D; C14-H01; C14-J01A3; C14-J01A4; C14-K01; C14-K01A; C14-N03; C14-N10; C14-N12; C14-N13;

C14-N14; C14-N16; C14-N17; C14-S01; C14-S04; C14-S06; C14-S08; C14-S12; D05-H11; D05-H12A; D05-H12B

TECH UPTX: 20001023

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred compounds: (I) Has mammalian aaT activity and is a substituted oxadiazole, thiadiazole or triazole peptoid. The antioxidant comprises vitamin A, E or C, OMEGA-3- or OMEGA-6- unsaturated lipids, alpha- or beta-carotene, superoxide dismutase, selenium and/or curcumin.

Preferred process: Method (IV) also includes administration of a thrombolytic agent or using a mechanical device to re-establish blood flow, especially (percutaneous transluminal) angioplasty. The aaT-like agent is a form of aaT resistant to inactivation by reactive oxygen intermediates.

ABEX UPTX: 20001023

SPECIFIC COMPOUNDS - About 85 compounds (I) are used e.g: (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (Ia).

39 NO oxide synthase inhibitors are used e.g: spermine.

ADMINISTRATION - (I) are administered to provide 1 ng-10 mg/ml of body fluid, and are delivered by osmotic pump, injection, orally, vaginally or rectally at intervals of 1 hour to 1 day, especially within 4 hours of an ischemic event. Dosage units contain 5-2000 (preferably 50-500) mg.

L114 ANSWER 11 OF 11 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-539813 [45] WPIX
CR 2000-611600 [58]
DNC C1999-157674
TI Increasing endothelial cell **nitric oxide** **synthase** activity in non-hypercholesterolemic patients.
DC B03
IN ENDRES, M; LAUFS, U; LIAO, J K; MOSKOWITZ, M A
PA (BGHM) BRIGHAM & WOMENS HOSPITAL INC; (GEHO) GEN HOSPITAL CORP; (BGHM) BRIGHAM & WOMENS HOSPITAL
CYC 84
PI WO 9918952 A1 19990422 (199945)* EN 52 A61K031-35
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9896934 A 19990503 (199945)
EP 1023060 A1 20000802 (200038) EN A61K031-35
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 6147109 A 20001114 (200060) A61K031-35
JP 2001519388 W 20011023 (200202) 61 A61K045-00
AU 2003203411 A1 20030612 (200456)# A61K031-35
US 2005038102 A1 20050217 (200514) A61K031-401
ADT WO 9918952 A1 WO 1998-US21464 19981009; AU 9896934 A AU 1998-96934 19981009; EP 1023060 A1 EP 1998-951041 19981009, WO 1998-US21464 19981009; US 6147109 A Provisional US 1997-62093P 19971014, US 1998-132848 19980811; JP 2001519388 W WO 1998-US21464 19981009, JP 2000-515587 19981009; AU 2003203411 A1 Div ex AU 1998-96934 19981009, AU 2003-203411 20030328; US 2005038102 A1 Provisional US 1997-62093P 19971014, CIP of US 1998-132848 19980811, Cont of US 1999-273445 19990319, US 2003-688721 20031015
FDT AU 9896934 A Based on WO 9918952; EP 1023060 A1 Based on WO 9918952; JP 2001519388 W Based on WO 9918952; US 2005038102 A1 CIP of US 6147109

PRAI US 1998-132848 19980811; US 1997-62093P 19971014;
AU 2003-203411 20030328; US 1999-273445 19990319;
US 2003-688721 20031015
IC ICM A61K031-35; A61K031-401; A61K045-00
ICS A61K031-195; A61K031-225; A61K031-365; A61K031-366; A61P001-00; A61P009-00; A61P011-00; A61P013-12; A61P015-10; A61P043-00
AB WO 9918952 A UPAB: 20050228
NOVELTY - Increasing endothelial cell **nitric oxide synthase** (ecNOS) activity in non-hypercholesterolemic subjects comprises administration of an 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor to increase ecNOS activity.

ACTIVITY - Antihypertensive; cardiant; vasodilator;

MECHANISM OF ACTION - HMG-CoA reductase inhibitor; Type III endothelial cell **nitric oxide synthase** upregulator.

The activity of ecNOS was assessed by measuring the LNMA-inhibitable nitrite accumulation from human endothelial cells. The ratio of nitrite to nitrate production under culture conditions was 5:1 and was similar for hypoxia and normoxia. Basal ecNOS activity at 20% oxygen was 6.0 plus or minus 3.3 nmol/500000 cells/24 hours. Exposure of endothelial cells to 3% oxygen for 34 hours decreased nitrite production by 75 plus or minus 14% (1.5 plus or minus 0.9 nmol/500000 cells/24 hours).

Treatment with simvastatin (1 mM) not only reversed completely the down regulation of ecNOS by hypoxia, but resulted in a threefold increase in ecNOS activity over basal activity (18 plus or minus 5.0 nmol/500000 cells/24 hours; p less than 0.05). This upregulation of ecNOS activity was attenuated by addition of L-mevalonate (400 mM) (9.6 plus or minus 1.3 nmol/500000 cells/24 hours). Interesting, simvastatin (1 mM) alone upregulated nitrite production fivefold (30 plus or minus 6.5 nmol/500000 cells/24 hours), which was blocked completely by L-mevalonate (400 mM) (8.6 plus or minus 2.9 nmol/500000 cells/254 hours). Similar findings were observed with lovastatin, but at 10-fold higher concentrations compared with those of simvastatin.

USE - Used to increase ecNOS activity in non-hypercholesterolemic, especially non-hyperlipidemic, subjects, to reduce brain injury resulting from stroke, to treat pulmonary hypertension, heart failure, progressive renal disease and to increase blood flow in tissues (claimed).

The method is also used to treat impotency, gastric and esophageal motility disorders, kidney disorders such as kidney hypertension, insulin deficiency and hypoxia-induced conditions including those induced by impaired lung function caused by emphysema, cigarette smoking, chronic bronchitis, asthma, infectious agents, pneumonitis (infectious or chemical), lupus, rheumatoid arthritis, inherited disorders such as cystic fibrosis, obesity and **alpha 1-antitrypsin** deficiency, as well as non-lung impairments e.g. from living at very high altitudes.

ADVANTAGE - The HMG-CoA inhibitor acts other than through preventing formation of oxidative LDL and increases **nitric oxide synthase** activity by effects directly on endothelial rather than hepatic HMG-CoA reductase.

Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: B04-L08; B07-A02B; B14-D05D; B14-E10A; B14-F01B; B14-F02B; B14-F02D; B14-K01; B14-N07; B14-N10; B14-N16; B14-P02
TECH UPTX: 19991103
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred method: The subject is non-hyperlipidemic and the amount of HMG-CoA reductase inhibitor is preferably less than the amount that alters blood low-density lipoprotein (LDL) cholesterol levels in the subject by 10%, but sufficient to increase

ecNOS activity above normal baseline levels.
The subject has a condition comprising an abnormally low level of ecNOS activity, which is hypoxia induced, chemically induced or cytokine induced. The subject has an abnormally elevated risk of or has pulmonary hypertension or has an abnormally elevated risk of or has experienced ischemic stroke. The patient is chronically exposed to hypoxic conditions. The method also comprises co-administering a non-HMG-CoA reductase inhibitor that increases ecNOS activity and an endothelial cell **nitric oxide synthase** substrate.
Preferred active agent: The HMG-CoA reductase inhibitor is simvastatin or lovastatin.

ABEX UPTX: 19991103
ADMINISTRATION - The dosage is 0.01-1000 (preferably 50-500) mg/kg/day, especially orally in single or divided doses. Administration may be oral, parenteral, subcutaneous, intravenous or intramuscular. Administration also may be by time-release, delayed-release or sustained-release delivery systems. Long-term, sustained release implant may be arranged to deliver therapeutic levels for at least 30 days, preferably 60 days. Administration may be in combination agents that are not HMG-CoA reductase inhibitors or ecNOS substrates, but that can increase ecNOS activity such as estrogens and angiotensin-converting enzyme inhibitors.

=> => fil medline
FILE 'MEDLINE' ENTERED AT 10:40:52 ON 06 DEC 2005

FILE LAST UPDATED: 3 DEC 2005 (20051203/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all

L119 ANSWER 1 OF 1 MEDLINE on STN
AN 1999255198 MEDLINE
DN PubMed ID: 10323598
TI Modulation of peroxynitrite- and hypochlorous acid-induced inactivation of **alpha1-antiproteinase** by mercaptoethylguanidine.
AU Whiteman M; Szabo C; Halliwell B
CS International Antioxidant Research Centre, University of London, Kings College.. matt.whiteman@kcl.ac.uk
SO British journal of pharmacology, (1999 Apr) 126 (7) 1646-52.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990712
Last Updated on STN: 19990712
Entered Medline: 19990623
AB 1. Peroxynitrite is a cytotoxic species that can be formed, among other mechanisms, by the rapid reaction of superoxide with nitric oxide. Peroxynitrite formation has been implicated in a wide range of neurodegenerative and chronic inflammatory diseases, as has the formation of hypochlorous acid by myeloperoxidase. 2. There is considerable interest in the development of peroxynitrite scavengers as therapeutic agents. The thiol compound mercaptoethylguanidine has been suggested to fulfil this role since it has recently been shown to be not only a potent inhibitor of inducible **nitric oxide synthase** but also a scavenger of peroxynitrite. Indeed, it has been shown to be protective in some experimental models of circulatory shock and inflammation at plasma levels in the approximate range 100-300 microM. 3. One protein inactivated by peroxynitrite is the major inhibitor of serine proteinases in human body fluids, **alpha1-antiproteinase** . At high (250-1000 microM) concentrations, mercaptoethylguanidine was found to be effective in preventing peroxynitrite-mediated tyrosine nitration and alpha1-AP inactivation. 4. By contrast, lower concentrations of mercaptoethylguanidine (1-60 microM) enhanced the inactivation of **alpha1-antiproteinase** by peroxynitrite. 5. At all concentrations tested (1-1000 microM), mercaptoethylguanidine decreased the inactivation of **alpha1-antiproteinase** by hypochlorous acid. 6. We suggest that products of reaction of mercaptoethylguanidine with peroxynitrite or peroxynitrite-derived products could cause damage to **alpha1-antiproteinase**, and possibly other proteins in vivo, whereas scavenging of hypochlorous acid by mercaptoethylguanidine could contribute to its anti-inflammatory action in vivo.
CT Dose-Response Relationship, Drug
*Enzyme Inhibitors: PD, pharmacology
*Guanidines: PD, pharmacology
Humans
*Hypochlorous Acid: PD, pharmacology
*Nitrates: PD, pharmacology
***Nitric-Oxide Synthase: AI, antagonists & inhibitors**
Research Support, Non-U.S. Gov't
Tyrosine: ME, metabolism
***alpha 1-Antitrypsin: DE, drug effects**
RN **1190-74-5 (2-mercaptoethylguanidine)**; 26404-66-0 (peroxynitric acid); 55520-40-6 (Tyrosine); 7790-92-3 (Hypochlorous Acid)
CN 0 (Enzyme Inhibitors); 0 (Guanidines); 0 (Nitrates); 0 (**alpha 1-Antitrypsin**); EC 1.14.13.39 (**Nitric-Oxide Synthase**); EC 1.14.13.39 (inducible **nitric oxide synthase**)

=> d his

(FILE 'HOME' ENTERED AT 08:41:04 ON 06 DEC 2005)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:41:17 ON 06 DEC 2005
L1 1 S (US20040220113 OR US20040220239 OR US20040220242)/PN OR (US20
E SHAPIRO L/AU

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L2          281 S E3-E22,E38

     FILE 'REGISTRY' ENTERED AT 08:44:29 ON 06 DEC 2005
L3            1 S 9041-92-3

     FILE 'REGISTRY' ENTERED AT 08:45:08 ON 06 DEC 2005

     FILE 'HCAPLUS' ENTERED AT 08:46:39 ON 06 DEC 2005
L4         5682 S L3
L5          252 S (ALPHA1 OR ALPHA 1)()TRYPSIN(L)INHIBIT?
L6         1636 S (ALPHA1 OR ALPHA 1)()(PROTEASE OR PROTEINASE)(L)INHIBIT?
L7         5862 S (ALPHA1 OR ALPHA 1)()(ANTITRYPSIN OR ANTI TRYPSIN OR ANTIPROT
L8         7762 S L4-L7

     FILE 'REGISTRY' ENTERED AT 08:48:21 ON 06 DEC 2005
               E NITRIC OXIDE/CN
L9            1 S E3
               E NITRIC OXIDE SYNTHASE/CN
L10           1 S E3
L11           3 S E48,E49,E58

     FILE 'HCAPLUS' ENTERED AT 08:49:05 ON 06 DEC 2005
L12       89859 S L9
L13       25812 S L10,L11
L14       30332 S NITRIC OXIDE()(SYNTHASE OR SYNTHETASE)
L15          39 S L8 AND L13,L14
L16          32 S L8 AND L12
L17          72 S L8 AND NITRIC OXIDE
L18          78 S L15-L17
L19           8 S L1,L2 AND L8
L20           4 S L1,L2 AND L12-L14
L21           5 S L1,L2 AND NITRIC OXIDE
L22           9 S L19-L21
               SEL RN L1

     FILE 'REGISTRY' ENTERED AT 08:51:31 ON 06 DEC 2005
L23          83 S E1-E83
L24          80 S L23 NOT L3,L9-L11
L25           1 S L24 AND UNSPECIFIED
L26          79 S L24 NOT L25

     FILE 'HCAPLUS' ENTERED AT 08:56:58 ON 06 DEC 2005
L27           8 S L22 NOT L1
L28           1 S L27 AND CLINICAL CONDITIONS
               SEL RN

     FILE 'REGISTRY' ENTERED AT 09:47:43 ON 06 DEC 2005
L29         117 S E84-E200
L30          19 S 55-63-0 OR 56-06-4 OR 71-44-3 OR 79-17-4 OR 124-20-9 OR 140-6
L31           8 S 53774-63-3 OR 57564-91-7 OR 66036-77-9 OR 74209-34-0 OR 79032
L32          27 S L30,L31
L33           1 S 151-16-6
L34          40 S 151-16-6/CRN
L35           1 S L34 AND H2O4S
L36           1 S 18144-22-4
L37           1 S L35,L36
L38           1 S 20933-81-7
L39           1 S 36889-13-1
L40           2 S 36889-13-1/CRN
L41           1 S 150403-88-6
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L42           1 S 156719-41-4
L43           4 S 156719-41-4/CRN
L44           2 S L43 AND CLH
L45           2 S 2986-19-8 OR 2986-20-1
L46         208 S (2986-19-8 OR 2986-20-1)/CRN
L47           6 S L46 AND H2O4S
                E DIPHENYLENEIODONIUM/CN
L48           1 S E3
L49          44 S 244-54-2/CRN
L50           5 S L49 AND CL/ELS
L51          41 S IC4-C6-C6/ES AND CL/ELS
L52          36 S L51 NOT L50
L53           7 S L52 AND 3/NR AND 1/NC
L54           1 S 75830-53-4
L55          51 S L32,L33,L35,L37-L42,L44,L45,L47,L48,L53,L54
L56          80 S L29 NOT L55
L57          45 S L56 NOT NC4/ES
L58           2 S L57 AND ACETATE
                E NG-MONOETHYL-ARGININE/CN
L59           1 S E6
L60           1 S E2
L61           2 S 20933-81-7/CRN
L62           1 S L61 AND ACETATE
L63           3 S L29 AND CLH
L64           2 S ARGININE/CN
L65           1 S L63 AND NITRO
L66           1 S HOMOARGININE/CN
L67           5 S L29 AND LYSIN?
L68           1 S L67 AND ACETATE
L69           9 S L29 AND NITRO
L70           3 S L69 AND ORNITHINE
L71           1 S L69 AND LYSINE
L72          56 S L55,L58,L60,L62,L65,L68-L70
                E HEMOGLOBIN/CN
L73           1 S E3
                E MYOGLOBIN/CN
                E CYTOCHROME/CN
                E CYTOCHROME 5/CN
                E CYTOCHROME V/CN
L74          57 S L72,L73

     FILE 'HCAPLUS' ENTERED AT 10:15:49 ON 06 DEC 2005
L75       71593 S L74
                SEL DN AN 6
L76         399 S L8 AND L75
L77          11 S L18 AND L76
L78           8 S L77 NOT 3/SC
L79           1 S L1,L2 AND L76
L80           9 S L22,L79
L81           1 S L1,L2 AND L75
L82           9 S L80,L81
L83           7 S L78 NOT L82
                SEL DN AN 6
L84           1 S L83 AND E1-E3
L85         388 S L76 NOT L77,L82
L86         376 S L85 AND (PY<=2003 OR PRY<=2003 OR AY<=2003)
L87          26 S L74(L)THU/RL AND L86
L88           0 S L87 AND L10,L11
L89           0 S L86 AND L10,L11
L90           0 S L14 AND L86
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     FILE 'HCAPLUS' ENTERED AT 10:29:34 ON 06 DEC 2005

     FILE 'EMBASE' ENTERED AT 10:31:04 ON 06 DEC 2005
L91      105095 S L75
L92       10227 S L8
L93         646 S L91 AND L92
L94           1 S L93 AND L10,L11
L95          10 S L93 AND L9
L96          10 S L94,L95
L97           8 S L96 AND PY<=2003
                SEL DN AN 4
L98           1 S L97 AND E7

     FILE 'EMBASE' ENTERED AT 10:33:30 ON 06 DEC 2005

     FILE 'WPIX' ENTERED AT 10:33:36 ON 06 DEC 2005
L99           3 S L1
L100        731 S L5/BIX OR L6/BIX OR L7/BIX
                E ALPHA/CN
                E ALPHA-1/CN
L101          2 S E10,E11
                SEL SDCN
                EDIT /SDCN /DCN
L102         93 S E1-E2
L103        741 S L100,L102
                E NITRIC OXIDE/CN
L104          1 S E5,E8,E10
                SEL SDCN
                EDIT /SDCN /DCN
L105         64 S E1
L106        970 S L14/BIX
L107          3 S L103 AND L105,L106
L108          8 S SHAPIRO L?/AU AND L103
L109          2 S SHAPIRO L?/AU AND L105,L106
L110          1 S L108 AND L109
L111          6 S L99,L107,L109,L110
L112          5 S L108 NOT L111
L113         10 S L111,L112 AND ?TRYPSIN?/BIX
L114         11 S L111,L113

     FILE 'WPIX' ENTERED AT 10:39:33 ON 06 DEC 2005

     FILE 'MEDLINE' ENTERED AT 10:39:56 ON 06 DEC 2005
L115      31578 S L75
L116      32431 S L14 OR L10 OR L11
L117       5886 S L115 AND L116
L118      11292 S L8
L119          1 S L117 AND L118

     FILE 'MEDLINE' ENTERED AT 10:40:52 ON 06 DEC 2005

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